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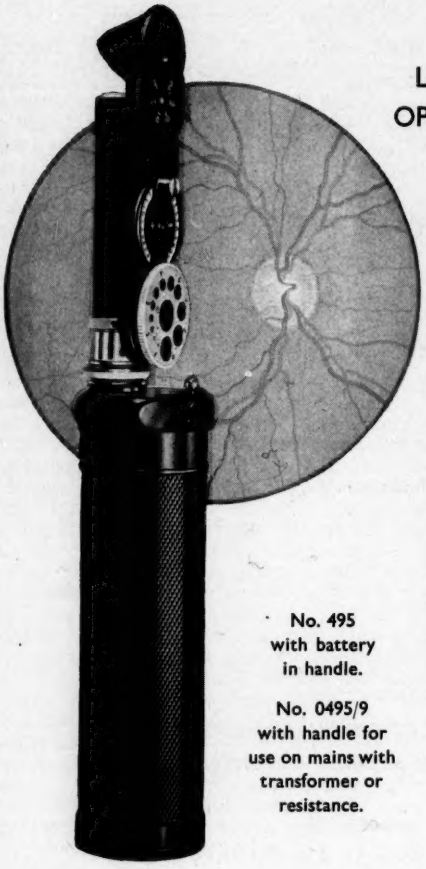

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COMMUNICATIONS

INFLUENCE OF THE FIFTH CRANIAL NERVE ON THE INTRA-OCULAR PRESSURE OF THE RABBIT EYE*†

BY

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INTRODUCTION

THIS paper is a continuation of previous studies on possible nervous mechanisms involved in the control of intra-ocular pressure in experimental animals, and has consisted, in the main, of recording the changes in intra-ocular pressure produced by cutting and stimulating the fifth cranial nerve in rabbits, with observations on the pupillary reaction, temperature changes in the eye, and the episcleral and choroidal vessels.

NORMAL INTRA-OCULAR PRESSURE

The mechanism whereby the normal intra-ocular pressure is maintained has excited the interest of physiologists and ophthalmologists ever since Mackenzie (1830) pointed out the association between an increase in this pressure and the disease known as glaucoma. A knowledge of the normal height of the intra-ocular pressure was an essential preliminary to investigation of its abnormalities, and many reports of measurements can be found in the literature.

These measurements can be divided into two groups; the first and smaller group was made by manometric methods, in which direct readings of the pressure were obtained by inserting a needle connected to a manometer into the anterior chamber.

Hering (1869) was one of the earliest workers to use a method of this type on human eyes. He employed a fine capillary tube sealed at one end and partly filled with saline to enclose an air column at the sealed end. A needle at the open end of the tube was introduced into the anterior chamber of an eye, thus allowing the intra-ocular pressure to cause a movement of the saline along the tube as the air was compressed. The difficulty of measuring the small movement of the saline made the method inaccurate.

Wahlfors (1888) also used a manometric method on a human eye before enucleation and found a pressure of 26 mm. Hg. Wessely (1916),

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during an investigation into the effect of contraction of the extra-ocular muscles on the intra-ocular pressure, obtained pressures of 22·5 and 18·5 mm. Hg in two human eyes before enucleation. Seidel (1922) recorded pressures of 25 and 20 mm. Hg in two human eyes, also before enucleation.

Manometric methods have also been applied extensively to animals, and the results show the average pressure to be in the region of 25 mm. Hg with extremes of 18 and 30 mm. Hg.

The second and larger group of measurements on human eyes has been made by tonometric methods. These results, by the very nature of the methods used, cannot claim to be as accurate as manometric measurements, but the average values obtained by most workers agree fairly well with the manometric results.

Schiötz (1909), the inventor of one of the most popular tonometers, considered the normal intra-ocular pressure to be between 19 and 30 mm. Hg. Cridland (1917) analysed the figures from eight publications and found an average of 19·1 with limits of 12·3 to 26 mm. Hg (Schiötz); in a personal series representing 1,001 normal eyes, he found an average of 20·06 mm. Hg. McLean (1919), using his own design of tonometer, obtained values of 22 to 40 mm. Hg for the normal range. Müller (1931) considered the normal range to be from 12 to 35 mm. Hg (Schiötz). Marlow (1949) examined 104 eyes, using both Schiötz and Harrington tonometers, and found an average pressure of 18·5 mm. Hg. Glees (1952) found values between 10 and 30 mm. Hg (Schiötz), with a mean value of 20·3, in a series of 5,392 eyes. Goldmann (1954), using an applanation tonometer of a new design, considered the average normal pressure to be 15·5 mm. Hg, but later quoted a figure of 14·5 mm. Hg (Goldmann, 1955). Jackson (1955), using an American standard Schiötz tonometer with a 7·59-g. weight, found an average tension of 24 mm. Hg (Schiötz) with a range of 10 to 40. Using the new calibration curves from the Report on Standardization of Tonometers of the American Academy of Ophthalmology (Friedenwald, 1954), these averages would be a little lower—22 mm. Hg with limits of 9 to 37 mm. Hg.

These figures show that, although the limits of normal pressure are wide, the average value is in the region of 20 mm. Hg. In spite of the considerable variation between individuals, the intra-ocular pressure of any single animal or person has always been found to remain remarkably constant under normal conditions, showing only small diurnal variations of 3 or 4 mm. Hg.

The discovery by Ascher (1942) and independently by Goldmann (1947) of episcleral vessels containing aqueous humour settled the long controversy whether or not there was a continuous flow of aqueous out of the eye. Their findings have been amply confirmed in human eyes by many workers, and aqueous veins have also been demonstrated in rabbits by Weekers and Prijot (1950) and by Greaves and Perkins (1951). Ashton (1951, 1952) and Ashton and Smith (1953) demonstrated the origin of these vessels from the

canal of Schlemm in man by means of Neoprene casts, and there is no doubt that a continuous formation and drainage of aqueous humour takes place in the normal eye.

While the mechanism of drainage of aqueous is now well established, the formation of aqueous is not so thoroughly understood. The original hypothesis of Duke-Elder (1927) that aqueous humour is formed by a process of simple diffusion from the plasma was later modified in the light of his work on the osmotic relationships of aqueous humour and plasma (Benham, Duke-Elder, and Hodgson, 1938; Duke-Elder, 1948) which showed that the aqueous humour was hypertonic to plasma. This hypertonicity must be due to the entry of some ion or ions by an active transfer from the plasma—*i.e.* secretion. The evidence at the present time suggests that two ions, ascorbate and bicarbonate, are secreted into the aqueous. The concentration of ascorbate in the aqueous humour was first shown by Müller and Buschke (1934), and this has been repeatedly confirmed by other workers, and as there is no evidence that ascorbic acid is synthesized within the eye it must enter by secretion.

Kinsey (1950) has shown that the bicarbonate content of the aqueous humour is higher than that of the plasma, and has suggested that this ion is primarily responsible for the hypertonicity of the aqueous humour. The aqueous humour/plasma ratio of all other ions so far investigated has been found to be less than unity, which is consistent with a bulk flow of fluid through the eye. It is thought that the aqueous humour originates in the ciliary processes, but water and some ions may enter and leave the anterior chamber through the capillaries of the iris.

Many estimations of the bulk flow of aqueous humour have been made in animals by injecting a test substance into the blood stream and measuring the steady-state ratio of concentrations in the aqueous humour and plasma. Para-aminohippuric acid is a suitable substance to use, as it is rapidly excreted by the kidney. Although there is some disagreement in details, the rate of flow has been found to be approximately 1 to 2 per cent. of the volume of aqueous humour per minute.

Similar estimations have been made on human eyes, using fluorescein as a test substance. A value of 1·9 $mm.^3$/min. was found by Goldmann (1955) using this method, while Grant (1955), using the entirely different method of tonography, obtained a value of 1·29 $mm.^3$/min.

It seems reasonable to suppose that the relative stability of the intra-ocular pressure is related, in part at least, to a controlled flow of aqueous, and, while a detailed discussion of ocular dynamics is outside the scope of this work, it is useful to consider some of the fundamental problems involved. Priestley Smith (1891) showed a very clear grasp of the essentials of the subject and laid a firm foundation for later workers. His book is outstanding for its clarity of thought and acuteness of observation.

First the basic process can be described as follows: blood enters the eye

by the force of the heart's action, fluid crosses the blood–aqueous barrier into the posterior chamber, and thence to the anterior chamber which it leaves *via* the angle of the anterior chamber and Schlemm's canal. Water and electrolytes may also enter and leave the anterior chamber through the capillaries of the iris. From Schlemm's canal the aqueous flows into the episcleral plexus and back into the blood stream, sometimes appearing in the conjunctival vessels where it can be seen in the aqueous veins. We know that under normal conditions the pressure of the intra-ocular fluid is kept constant within wide limits, and that changes induced in this pressure, for example, by massaging the globe, are quickly counteracted.

Such a tendency to maintain a constant pressure could be effected by a number of factors or combination of factors. An increased capillary pressure, an increased secretion or an increase in the osmotic pressure of the aqueous humour, a narrowing of the exit channels, or a rise in episcleral venous pressure are all factors tending to increase the pressure. Similarly a decreased capillary pressure, a decreased osmotic pressure of aqueous, widening of the exit channels, or a lowering of the episcleral venous pressure would tend to decrease the intra-ocular pressure. Possible resistance to flow through the trabeculae must also be taken into account, as changes in its resistance could alter the rate of flow of aqueous and thereby alter the intra-ocular pressure.

That all these factors combine in a harmonious way to produce a steady intra-ocular pressure strongly suggests that an active compensating mechanism exists. It is worthwhile, however, to consider whether a static system depending only on fixed anatomical relationships could in fact produce a stable intra-ocular pressure in spite of random variations in any or all of these factors.

The anatomical arrangement can be represented diagrammatically as in Fig. 1 (opposite).

Here *A* represents the arterial supply to the eye, *C* the capillary network, *V* the veins, *E* the anterior and posterior chambers separated from the capillaries by a semi-permeable membrane *M* (the blood–aqueous barrier), and *S* the drainage channels back to the veins, separated from *E* by the trabeculae *T*.

The hydrostatic pressure in *A* would tend to push the fluid through the membrane into *E* and, providing the pressure in *E* was greater than that in the veins, fluid would leave *E* through *T* and *S* into *V*.

How would such a system react to enforced changes in pressure within *E*? A rise in pressure in *E* would decrease the hydrostatic difference on either side of *M*, tending to decrease inflow, and would increase the rate of flow through *S*, resulting in the desired effect of reducing the pressure. Conversely, a reduction in pressure in *E* would automatically increase the fluid entry and decrease the outflow. Presuming the correct ratios of size between the arteries, veins, and exit channels, such a system would provide a self-

regulatory mechanism for keeping the pressure in *E* constant. The height of the pressure would depend on the relative pressures in *A* and *V*, and the degree of permeability of *M*, the resistance of *T*, and the size of the exit channels.

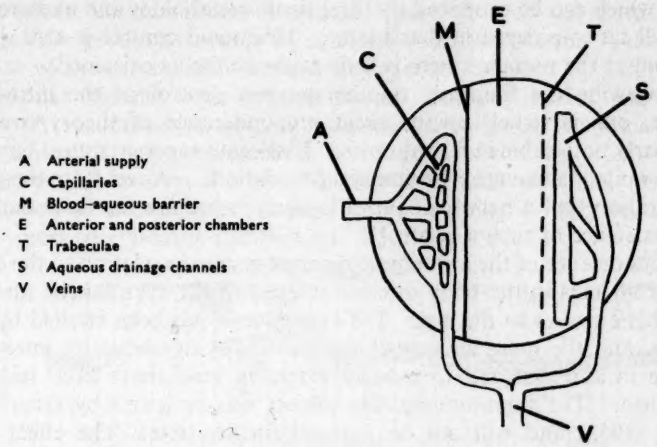

FIG. 1.—Diagram of aqueous flow.

It is probably fair to use such a mechanical analogy to explain the broad principles of control of the intra-ocular pressure, but the system is found to be deficient when the details of the actual apparatus as found in the eye are considered. First, the blood vessels are very different from a rigid system of tubes, and it is probably true that the capillary bed of the ciliary body which brings the blood into contact with the blood–aqueous barrier is never fully open or closed, but that different areas are dilated or contracted in a constantly varying proportion.

Secondly, it has been shown that aqueous humour is produced by a process involving secretion—an activity which is always under some form of central control—either hormonal or nervous; and thirdly, it must be remembered that aqueous humour is not solely concerned with the maintenance of intra-ocular pressure, but has metabolic duties to perform in relation to such avascular structures as the lens and cornea.

It would then be remarkable if no form of control over the formation and flow of aqueous and the intra-ocular pressure existed.

Some of the experimental evidence has been presented by the author in a recent paper (Perkins, 1955).

POSSIBLE MECHANISMS FOR CONTROL OF INTRA-OCULAR PRESSURE

Once the need for a controlling mechanism is admitted, it is natural to consider the central nervous system as a possible participant, though it

must be borne in mind that considerable autonomy exists in the peripheral vascular system independently of the central nervous system. Lewis and his co-workers (Lewis and Grant, 1924; Lewis, 1926; Lewis, Harris, and Grant, 1927) have shown the very marked changes in peripheral vascular pattern which can be produced by local tissue metabolites and axon reflexes; these will be considered in detail later. Hormonal control is also a possibility, but at the moment there is little evidence for its existence.

In reviewing the literature on the nervous control of the intra-ocular pressure, one is struck by the great preponderance of theory over fact, particularly noticeable in recent times. Elaborate superstructures have been built on quite inadequate experimental foundations. Apart from the general consideration that a nervous control is likely, what are the facts that point to the existence of such a control?

The importance of the autonomic nervous system in relation to the control of other systems in the body directed interest to the sympathetic and parasympathetic nerves to the eye. The sympathetic has been studied by many workers, and the main actions of the cervical sympathetic on intra-ocular pressure in animals (and to a lesser extent in man) have been fairly well established. The literature on this subject was reviewed by Greaves and Perkins (1952) and will not be pursued further here. The effect of the sympathetic as demonstrated by our experiments can be summarized briefly under three headings:

(1) First to be considered is its adventitious effect, by which is meant its effect on the smooth muscle in the orbit, a contraction of this muscle causing a passive rise in intra-ocular pressure and its relaxation a slight fall. Such changes are not important and show much variation between species. In the cat, for example, an initial rise due to this process can be demonstrated by stimulating the cervical sympathetic, while in the rabbit, with less smooth muscle in the orbit, this initial rise is absent.

(2) The second and probably the most important effect is the vasoconstriction of the ocular blood vessels. Most of the workers in this field have been content to record changes in the intra-ocular pressure only, and observations on the vessels themselves have rarely been made. Greaves and Perkins (1952) studied and photographed the effect of sympathetic stimulation on the choroidal vessels, the episcleral vessels, and the vessels of the ciliary plexus. We found a marked vasoconstriction of the ciliary vessels and only slight changes in the choroidal vessels. The technique of observing the choroidal vessels will be described in detail later. Wudka and Leopold (1956) reported narrowing of the long ciliary arteries after stimulation of the sympathetic in the rabbit.

(3) The sympathetic may have an effect on the capillary permeability. Such a change has been reported by Engel (1941) in the knee joint, as shown by the rate of entry of a dye into the synovial fluid from the blood stream,

and an increase in the permeability of the blood–aqueous barrier after section of the sympathetic has been described by Müller and Pflimlin (1929) and by Hallermann, Basch, and Ladeburg (1951).

As far as the parasympathetic is concerned there is no evidence of any direct effect on intra-ocular pressure. Stimulation of the third nerve in rabbits does produce a rise in intra-ocular pressure, but this is due to contraction of the extra-ocular muscles and can be abolished by paralysing the extra-ocular muscles with decamethonium iodide (Greaves and Perkins, 1953). A vasodilatation of pial vessels on stimulating the vagus and the seventh cranial nerve in monkeys has been reported by Chorobski and Penfield (1932) and by Forbes, Nason, Cobb and Wortman (1937), but stimulation of these nerves has been found to have no effect on the intra-ocular pressure (Greaves and Perkins, 1956; Fig. 2).

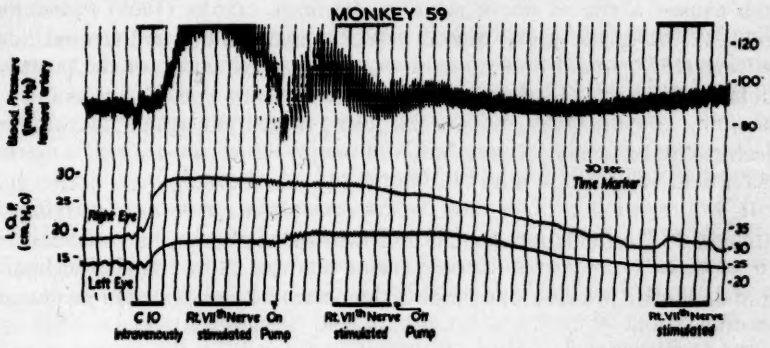

FIG. 2.—Recording of blood pressure (*upper trace*) and intra-ocular pressure of right eye (*middle trace*) and left eye (*lower trace*) of a monkey. *Injection of C.10 causes a tonic* contraction of the extra-ocular muscles resulting in a rise in intra-ocular pressure. *Stimulation of the right seventh nerve produced no change in intra-ocular pressure.*

The only evidence for a parasympathetic action on intra-ocular pressure seems to be the fact that inhibition of cholinesterase by drugs reduces the *intra-ocular pressure in glaucoma.* In the normal eye, however, eserine tends to cause a slight and temporary increase in the pressure, probably owing to capillary dilatation, and the presence of a parasympathetic control has yet to be proved.

Some experimental evidence for a controlling centre in the diencephalon has recently been put forward (von Sallmann, Macri, Wanko, and Grimes, 1956; Gloster and Greaves, 1956).

There is, therefore, some evidence that the autonomic nervous system may play a part in the control of intra-ocular pressure through sympathetic pathways.

One other type of vascular response associated with nervous activity is found in relation to the sensory nerves, and the present study was undertaken to determine whether vascular changes leading to changes in intra-ocular

pressure could be mediated by the sensory supply to the eye. The literature on vascular changes associated with peripheral sensory nerves will first be reviewed, followed by that concerning changes in the eye after stimulation of the fifth cranial nerve, both by direct stimulation of the nerve trunk and by trauma to the eye.

Vascular Reflexes involving Peripheral Sensory Nerves Generally

Stimulation of a peripheral sensory nerve may give rise to antidromic vasodilatation, either by a special kind of afferent fibre ending in the capillary walls, or by metabolites set free in cells by impulses passing down afferent nerve fibres (Langley, 1923). The earliest observations of this type were made by Schiff (1855), who noticed that section of nerve roots supplying a limb caused a rise in temperature in the limb. Goltz (1869) found that crimping the sciatic nerve caused a rise in temperature in the hind limb. Stricker (1877) found that stimulation, mainly mechanical, of the posterior roots of the nerves to the hind limb also caused a rise in temperature in the limb. Bayliss (1900, 1901, 1902), using a plethysmograph, showed that electrical and mechanical stimulation of the posterior roots caused a marked increase in volume of a hind limb in the cat.

It is interesting to note that Bayliss found that, in spite of varying the strength of the induction current and the rate of shocks, he could not rely on electrical stimulation causing vasodilatation in a limb. Mechanical stimulation by pricking or crimping the nerve, however, always produced a vasodilatation.

Bruce (1910) observed that an irritant substance, such as oil of mustard, applied to the conjunctiva caused dilatation of the vessels, but that no dilatation occurred after degeneration of the sensory nerves to the conjunctiva. Bruce postulated a division of sensory fibres at the periphery, one part coming from the normal sensory ending, the other division going to the local arterioles where it causes reflex vasodilatation when the sensory ending is stimulated. This postulate has been substantiated by the work of Adrian, Cattell, and Hoagland (1931). They recorded action potentials travelling peripherally in a sensory nerve when skin supplied by a higher branch of this nerve was stimulated.

Bardy (1915) in the main confirmed the results of Bruce, but found the effect much reduced after repeated local instillation of 2 per cent. nicotine or intravenous injection of 60 mg. nicotine. As Langley (1923) points out, nicotine in this dosage would cause a large drop in blood pressure which in itself is likely to prevent a hyperaemic response. The importance of a reasonably normal general blood pressure for the maintenance of these effects is shown by the fact that, though nitrogen mustard normally causes a gross rise in intra-ocular pressure when injected subconjunctivally in the rabbit, the reaction does not occur if the blood pressure is kept below

approximately 90 mm. Hg by deep anaesthesia (Davson and Perkins, unpublished).

Yasukazu Doi (1920) demonstrated antidromic fibres in the posterior roots of spinal nerves of the frog. Stimulation of these fibres caused dilatation of skin vessels.

Feldberg (1926) reported that mechanical and electrical stimulation of the auricularis, ventralis, and dorsalis nerves to the rabbit ear after sympathectomy produced a vasodilatation after a latent period of 10 to 15 seconds.

Lewis and Marvin (1926) also reported vasodilatation of skin vessels lasting 5 to 10 minutes after stimulation of a sensory nerve. They considered the antidromic vasodilatation to be due to impulses along the sensory nerves, not to the vessels directly but to the tissues of the skin, where these impulses caused the release of some substance which acted on the vessels.

Holton and Perry (1951) showed that, in the ears of sympathectomized rabbits, a consistent and reproducible vasodilatation was obtained in response to stimulation by single or multiple shocks applied to the peripheral end of the cut greater auricular nerve. The response to single shocks came on after a latency of about 10 seconds. The stimulation, using a unipolar saline cotton wool electrode, had to be of 15 volts and 10 millisecond duration. This antidromic vasodilatation was depressed by eserine, and this depression was reversed by atropine.

Weddell (1954), using improved histological techniques, was able to demonstrate that peripheral sensory nerves to the skin split up into numerous nerve fibres which are branches of parent fibres and may be myelinated or non-myelinated. In some cases myelinated fibres lose their myelin sheaths and travel for several millimetres as non-myelinated fibres before giving rise to a profuse arborization of fine, freely ending, naked, axoplasmic filaments. These filaments may terminate in unencapsulated nerve endings, encapsulated nerve endings, or endings related to hair follicles. Thus a complex plexus of branching axons is present in the skin and some of the branches are noted to end in relation to walls of arteries, arterioles, and venules.

There is, therefore, good physiological evidence and some anatomical evidence that the skin is supplied by antidromic fibres running with the sensory nerves and that stimulation of these fibres causes vasodilatation.

Literature on the Fifth Cranial Nerve as related to the Eye

Remarkably little has been written concerning the relationship between intra-ocular pressure and the fifth cranial nerve in experimental animals, and, apart from Hartmann's work, which will be described later, few clinical observations appear in the literature.

Magendie (1824), investigating the functions of the cranial nerves in rabbits, cut the fifth nerve and noted contraction of the pupil followed by loss of sensation on the affected side of the face. Bernard (1858) also

found that cutting the nerve in rabbits caused miosis, increased vascularity, and dullness of the cornea with increased curvature.

Budge and Waller (1852) described the following experiment:

In a man who was recently decapitated in this town on 12th December, we have immediately after the event, stimulated galvanically the sympathetic nerve and produced a marked dilatation of the pupil. After the stimulation was stopped the pupil gradually recovered to the previous state. After repeating these experiments several times the third nerve was exposed and stimulated. This caused a contraction of the pupil and movements of the globe. Galvanic stimulation of the fifth nerve did not give a result when applied to the gasserian ganglion or behind this body, but when applied in front of the ganglion caused dilatation of the pupil. Electrical stimulation of the globe caused a contraction of the pupil followed immediately by a dilatation.

Donders (1864), investigating whether division of the fifth nerve interrupted the sympathetic supply to the eye in the rabbit, obtained the following results:

(1) Division of the nerve at or distal to the ganglion caused contraction of the pupil which diminished within a few hours.

(2) The tension of the eyeball remained at first the same, sometimes becoming even rather greater while the pupil was small, but later becoming lower than normal providing the eye remained quiet.

(3) After division of the fifth nerve, stimulation of the sympathetic nerve in the neck still produced a dilatation of the pupil in seven out of eleven animals, though the dilatation was much slighter in degree. In the other four animals the dilatation was absent. In all the animals the cornea was insensitive, but in four of the animals showing some dilatation one or other lid was still sensitive.

Von Hippel and Grünhagen (1868) passed a strong electric current through electrodes placed on either side of the medulla at the roots of the fifth nerves and found a marked rise of intra-ocular pressure in rabbits. As Henderson and Starling (1904) point out, the unselective method of stimulating and the absence of blood pressure records leave these results open to other interpretations.

Von Schultén (1884) also reported that, although cutting the fifth nerve had no effect on intra-ocular pressure, stimulating the nerve did produce a marked rise in intra-ocular pressure. Again, no blood pressure records were taken, and the results of stimulating the gasserian ganglion by Bellarminoff (1886) are subject to the same criticism. Vulpian (1885) recorded vasodilatation in the eyes of dogs after stimulation of the fifth nerve.

Morat and Doyon (1902) and François-Franck (1875) found a fall in intra-ocular pressure on cutting the fifth nerve post-ganglionically and a rise in intra-ocular pressure on stimulating the nerve in animals. Angelucci (1893) noticed a reduction in ocular tension after extirpation of the ganglion in man, and Wilbrand and Saenger (1900) reported that excitation of the nerve increased the intra-ocular pressure.

Henderson and Starling (1904), working with cats, divided the fifth nerve between the gasserian ganglion and the brain and stimulated the ganglion with needle-electrodes. They found that stimulation caused a small rise in intra-ocular pressure, but this was accompanied by retraction of the nictitating membrane and dilatation of the pupil, showing that sympathetic fibres travelling in the ganglion were also being stimulated. When this experiment was repeated in animals which had had the cervical sympathetic cut some 3 to 4 weeks previously, no change in intra-ocular pressure was recorded. The general blood pressure was unaffected by stimulating the ganglion provided the pre-ganglionic section was complete.

Corrado (1951) found that stimulation of the fifth nerve in dogs caused an increase in vascularity of the eye and an exudate of protein into the anterior chamber. Quantitative determinations of histamine were made on the aqueous of such eyes. Histamine was absent in those eyes in which the first division of the fifth nerve had been sectioned and stimulated electrically. The histamine content of the opposite eye was normal. He explained these changes by an inhibitory action of the albumin which appears in large amounts as a result of increased vascular permeability of the eye on the stimulated side.

The increases in intra-ocular pressure recorded in some animals on stimulating the fifth nerve have been brought forward as evidence that the nerve contains vasodilator fibres to the eye, but, as Hartmann (1924) pointed out, a similar peripheral vasodilatation can be obtained by stimulating any sensory nerve.

Hartmann studied the effects of retro-gasserian section of the fifth nerve in man and found the following results:

(1) Slight enophthalmos and narrowing of the palpebral fissure.

(2) Miosis appearing 3 to 4 days after operation and lasting more than one year in the majority of cases.

(3) Dilatation of the pupil with cocaine and adrenaline enhanced on the operated side.

(4) A drop in intra-ocular pressure (averaging 4 mm. Hg) in the great majority of cases in the days following operation.

(5) A reduced retinal arterial pressure, as measured by Bailliart's method of ophthalmodynamometry, in most cases.

(6) Vasodilatation of the skin vessels in 80 per cent. of cases immediately after the operation. In old cases no obvious dilatation of skin vessels was observed, but pinching the skin produced a greater degree of vasodilatation on the operated side than on the normal side.

Hartmann considered that these effects were due to increased irritability of the peripheral axon reflex following loss of central control—a liberation phenomenon.

He concluded that there are no fibres from the autonomic nervous system in the fifth nerve; in particular no pupillary fibres, no vasomotor fibres for

the retina or skin of the face, and no fibres regulating ocular tension. The results which immediately follow section of the nerve can be interpreted as a release from central inhibition by the interruption of their sensory route to the brain. The changes in the days immediately following operation can be due partly to interruption of the nerve, but also to irritation of the cut end. Hartmann noted that these changes are all similar to those produced by an increase in parasympathetic tone. It would seem more likely that a decrease in sympathetic tone caused by section of sympathetic fibres in the ganglion was the cause of the changes he described.

To enable any form of central nervous control to act, some afferent pathway to inform the central nervous system of the state of the intra-ocular pressure must be postulated. There is some evidence that such a pathway exists in the fifth nerve. Dieter (1940) demonstrated action potentials in the fifth nerve on changing the intra-ocular pressure, and Tower (1940) reported background spike potentials from the long ciliary nerves of the cat, which disappeared after paracentesis.

The early workers (Donders, 1864; von Schultén, 1884; Morat and Doyon, 1902; François-Franck, 1875) reported that stimulation of the nerve in animals (mainly rabbits) caused a rise in intra-ocular pressure, and Magendie (1824), Bernard (1858), and Donders (1864) also noticed a contraction of the pupil.

The careful work of Henderson and Starling (1904) on cats demonstrated that in this animal no such pupillary or intra-ocular pressure changes occurred provided the sympathetic fibres had degenerated. They also suggested that the rise in intra-ocular pressure claimed by other workers could have been due to rises in general blood pressure. It is a pity that Henderson and Starling did not repeat these experiments on rabbits, as their authoritative opinions, based only on cat experiments, may partly account for the lack of interest in the fifth nerve as related to intra-ocular pressure since their work was published. It is also probable that the technical difficulties involved in the surgical approach to the fifth nerve in rabbits has also been a factor in this lack of interest.

Changes in Intra-Ocular Pressure induced by Trauma

It is reasonable to suppose that trauma to the eye causes strong stimulation of the sensory endings of the fifth nerve, and it is interesting to consider the effect of trauma on the intra-ocular pressure and intra-ocular circulation.

That trauma to the eye itself may cause disturbances of the intra-ocular pressure is well known. Clinically, a blow on one eye may result in a higher or lower tension in this eye followed by a period of instability of tension. Consensual changes in the other eye have also been reported; for example, in eyes with a predisposition to congestive glaucoma, operation on one eye may precipitate an acute attack in the other.

In animals, Wessely (1900), Magitot (1923), Leplat (1924), and Duke-

Elder and Duke-Elder (1931) obtained very similar results after trauma to the eye in one form or another. Magitot found that contusion of one eye was followed by a rise in intra-ocular pressure, which was sometimes accompanied by a contralateral change. Irritation of the iris or cornea produced a rise in tension with protein exudation in the aqueous.

Leplat found that contusion of one eye in rabbits caused a rise in tension in the injured eye and also a rise in the other eye, though to a lesser degree. The effects were most noticeable in unanaesthetized animals. Protein was frequently found in both aqueous humours even when a rise in pressure occurred only in the injured eye. Cocainization of the eye reduced the effect, and retrobulbar cocaine prevented any contralateral effect. The pupil contracted after the blow, but not necessarily in relation (of degree) to the rise in tension.

Duke-Elder found that scratching the iris caused a local vasodilatation accompanied by an increase in capillary permeability and a rise in intra-ocular pressure. He considered the changes to be comparable to the "triple response" described by Lewis (1924), which takes place in the skin after injury. Cocaine was found to prevent such changes.

Hallermann, Basch, and Ladeburg (1951) found that the application of ultrasonic radiations to the cornea of animals only produced a rise of intra-ocular pressure if the dose was great enough to cause opacity of the cornea.

Kornbluth and Linnér (1955) reported that performing tonography, in which a weighted tonometer is applied to one eye, caused a lowering of tension in the opposite eye of rabbits. Akagi, Nishimura, and Yamamoto (1955) found consensual changes in intra-ocular pressure after the artificial raising of the pressure in one eye, and that these were abolished by cutting the ophthalmic branch of the fifth nerve on the operated side.

Experiments on human eyes have shown similar results to those obtained in animals. Magitot (1939) described consensual changes after compression of the eye with a weight of 250 g. for 8 minutes. Such pressure caused a reactionary rise in the compressed eye and in some cases a consensual rise in the other eye.

Thomassen (1946) gave a comprehensive review of the literature relating to compression of the eye, and in his own experiments found occasional consensual rises when a reactionary rise in pressure followed compression of one eye.

Moreu (1948) reported that the rise of pressure after trauma to the eye (burns of the cornea and conjunctiva) was greater if the sympathetic supply had been previously cut.

We (Greaves and Perkins, unpublished) have attempted to explore the contralateral changes in the intra-ocular pressure of the rabbit eye after contusion. We had hoped to produce such a consensual effect in experimental

animals enabling an investigation of any nervous pathways involved. Although some interesting results were obtained, it was not possible to get sufficiently reliable effects for it to be worthwhile extending the experiments at present. It is probable that individual animals vary in their sensitivity and vasomotor reflex activity, and until a method of predetermining such vague properties is developed, further work must remain in abeyance.

Our experiments demonstrate that consensual changes do occur, but to a significant degree in only about 20 per cent. of animals. The changes which were recorded are of some interest, and a short account of the methods used and results obtained follows.

Dynamometry

Method.—For dynamometer experiments the animals were anaesthetized with Nembutal 1 g./lb. body weight intravenously for rabbits, and 1 g./1·5 lb. body weight intraperitoneally for cats. The femoral blood pressure and intra-ocular pressure of both eyes were recorded photographically by the apparatus to be described later.

In the dynamometer experiments pressure was then applied to one eye, using a Bailliart dynamometer, taking care not to drive the needle in the anterior chamber into the iris or lens. A pressure of 150 g. was used in all experiments, except two, where pressures of 50 and 140 g. respectively were used. The time of application is shown in Table I.

TABLE I
DYNAMOMETER EXPERIMENTS

Animal	No.	Pressure Applied (g.)	Length of Time of Application (sec.)	Change in Intra-Ocular Pressure (cm. saline)	
				Ipsilateral Eye	*Contralateral Eye*
Rabbit	240	50	50	Rise 10	No change
	74	150	50	Rise 30	No change
	134	150	60	Rise 50	Rise 2·5
	124	150	300	Rise 30	No change
Cat	10	150	240	Rise 12	No change
	79	150	30	Rise 12	No change
	34	150	300	Rise 15	No change
	11	150	120	Rise 5	No change
	33	150	180	Not recorded	No change
	43	140	120	No change	No change
	43	150	90	Rise 20	No change

Results.—It is apparent from the results that simple compression will produce a reactionary rise in the eye compressed after the pressure is released (Table I). In only one animal was any change relative to the compression seen in the intra-ocular pressure of the contralateral eye.

Impulse Stimulation

In an attempt to elicit a contralateral effect, a more violent method of stimulating the eye was tried. It was also decided to use urethane as an anaesthetic in case Nembutal was depressing any nervous reflexes involved. Doses of 1·75 g./kg. intravenously were used.

Method.—Under urethane anaesthesia, a spring-loaded plunger was held in apposition to an animal's eye so that on release of the spring a severe blow was transmitted to the eye. The distance of travel of the plunger could be regulated so that it did not deform the cornea more than eighth of an inch. The blood pressure and intra-ocular pressure of each eye was recorded as before.

Results.—Table II (overleaf) shows that a rise in the intra-ocular pressure of the injured eye was obtained in almost all experiments, though in many cases the blow had to be repeated once or twice. Faulty technique, in that the plunger was not sufficiently close to the cornea to transmit the impulse fully, probably accounts for the necessity to repeat the blow in some experiments, but in others it did appear that the first blow had less effect than the second blow repeated some minutes later.

In the 28 experiments, an average rise in pressure of 30 cm. saline was produced in the injured eye, but in only thirteen experiments was a significant change in intra-ocular pressure of the contralateral eye observed. Of these thirteen, a rise in intra-ocular pressure was noted on four occasions, in six a drop occurred, and in the remaining three a fall was followed by a rise of approximately the same amount. Five animals had a left sympathectomy performed immediately before the impulse stimulation, five received a retrobulbar injection of procaine, and two were given injections of strychnine. None of these manoeuvres gave any indication of increasing or decreasing the incidence of contralateral effects.

When such a change did occur it often took the form of a slow rise of pressure starting some 20 to 40 minutes after the initial stimulation. In some experiments the rise was preceded by a slow fall. The contralateral changes were, therefore, in the opposite direction to the changes in the stimulated eye (Fig. 3*a*, *b*, *c*, overleaf), the initial fall occurring during the rise of pressure in the stimulated eye, and the consensual rise occurring during the falling phase in the stimulated eye.

Consensual changes occurred in two out of five experiments in spite of a retrobulbar injection of 1 ml. procaine 2 per cent. before stimulation of the eye.

Summary.—The above experiments and those of other workers show, therefore, that trauma to the eye is followed by a rise in intra-ocular pressure in the injured eye and may cause a change in the contralateral eye.

Techniques

The techniques involved in this work fall into the following groups:

(*a*) Observational;
(*b*) Recording of intra-ocular pressure, blood pressure, and temperatures;
(*c*) Operative procedure in survival experiments;
(*d*) Histological.

(a) Observational

(*i*) *Episcleral Vessels* (*Animals*).—The lids were retracted with sutures and when necessary the eye was positioned by a corneal stitch. The episcleral vessels were

TABLE II

IMPULSE STIMULATION EXPERIMENTS

Rabbit No.	Side of Previous Sympathectomy	Impulses Applied		Change in Intra-Ocular Pressure (cm. saline)	
		Side	No.	*Ipsilateral Eye*	*Contralateral Eye*
34	—	Right	2	Rise 20	No change
59	—	Right	3	Rise (needle blocked)	
87	—	Right	2	Rise 40	Rise 12
28	—	Right	1	Rise 40	Rise 2
92	—	Right	2	Rise 23	Rise 10
212	—	Right	2	Rise 20	Fall 8 followed by Rise 5
142	—	Right	1	Rise 2	Fall 4
45	—	Right	2	Rise 50	No change
51	—	Right	2	Rise 15	Fall 3
63	—	Right	1	Rise 17	No change
216	—	Right	2	Rise 27	Fall 3
133	Left	Right	1	Rise 10	Fall 10
103	Left	Left Right	1 1	Rise 45 Rise 5	No change No change
28	Left	Right	2	Rise 20	Fall 5 followed by Rise 5
35	Left	Right	2	Rise 33	Rise 10
62	Left	Right	3	Rise 25	Fall 2
61	—	Right	1*	Rise 45	No change
205	—	Right	1*	Rise 9	Rise 13
200	—	Right	1*	Not recorded	No change
148	—	Right	2*	Rise 7	Fall 5
134	—	Right	1*	Rise 16	No change
141	—	Left	2	Rise 50	No change
6	—	Left	1	Rise 20	No change
35	—	Left	1	Rise 20	No change
45	—	Left	1†	No change	No change
43	—	Left	1†	No change	No change

* After retrobulbar procaine

† After strychnine

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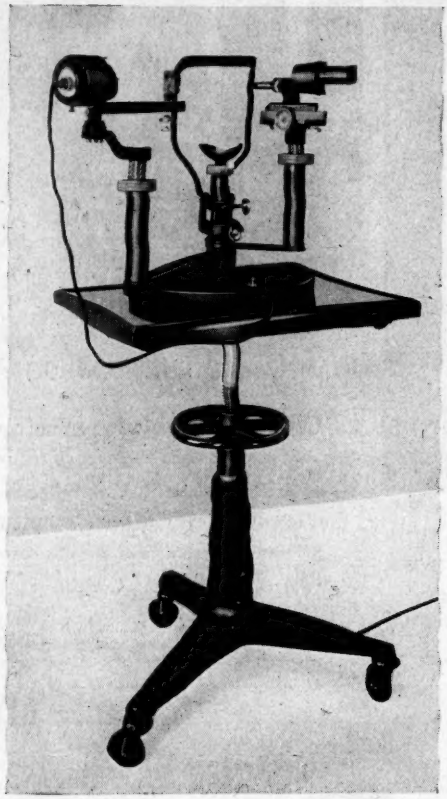

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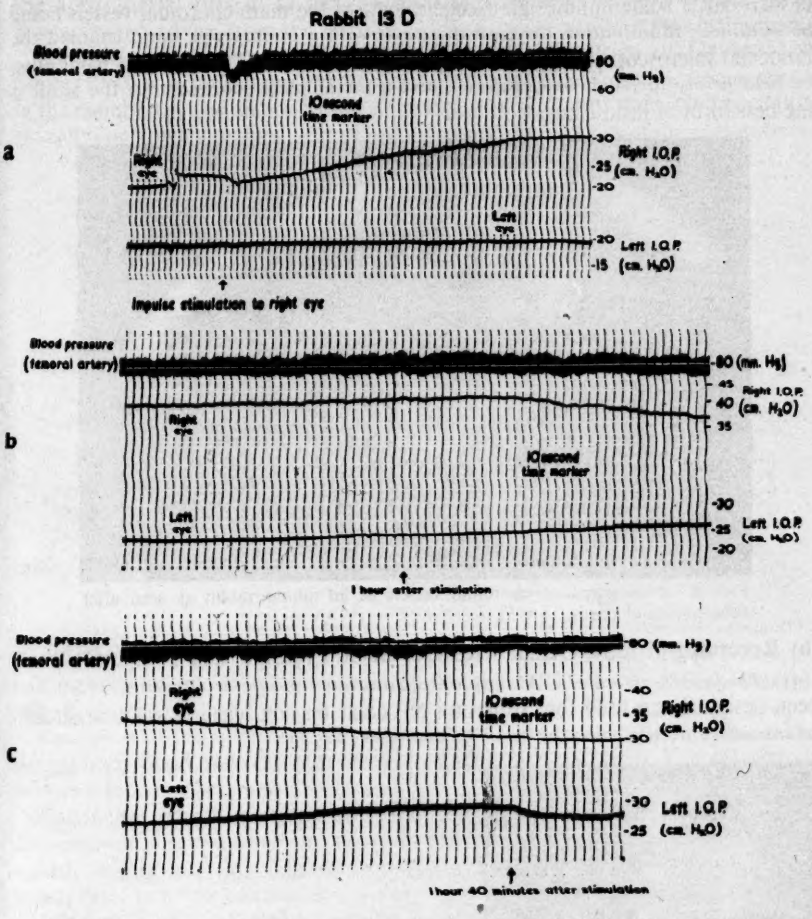


FIG. 3 (*a*).—Recording of blood pressure and right and left intra-ocular pressures of a rabbit. Right intra-ocular pressure begins to rise after impulse stimulation to this eye. Left intra-ocular pressure remains unaltered.

FIG. 3 (*b*).—The right intra-ocular pressure has now reached 40 cm. saline, but not until nearly one hour after stimulation does the left intra-ocular pressure start to rise.

FIG. 3 (*c*).—The right intra-ocular pressure is falling while the left intra-ocular pressure continues to rise, reaching a level of 30 cm. saline.

observed with a binocular microscope and photographed with a Kiné-Exacta camera fitted with a long extension tube, illumination for photography being obtained from an electronic flash apparatus.

(ii) *Choroidal Vessels* (*Animals*).—It has been previously reported (Greaves and Perkins, 1952) that the sclera can be made transparent by dehydration. The conjunctiva was reflected from the sclera in albino rabbits and dried by a current

of air. After some minutes an excellent view of the main choroidal vessels could be obtained; illumination through the pupil with a microscope lamp enabled the binocular microscope to be used and photographs taken (Fig. 4). The head must be held firmly for such observations, and a metal plate screwed into the skull is the best form of head clamp.

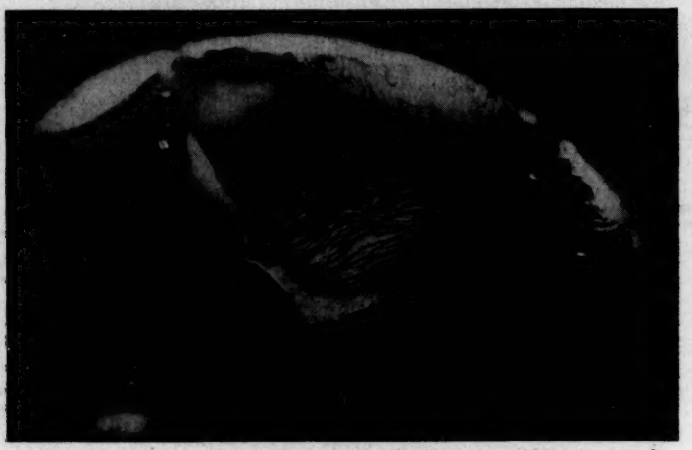


FIG. 4.—Photograph of choroidal vessels of an albino rabbit as seen after dehydration of sclera. (× 5).

(b) Recording of Intra-Ocular Pressure, Blood Pressure, and Temperature

(*i*) *Tonometric Method.*—A simple applanation tonometer (Perkins, 1953) has been designed and used for estimation of ocular tension when it was undesirable to introduce needles into the anterior chamber (Fig. 5).

FIG. 5.—Photograph of applanation tonometer. The brass ring in the foreground is an additional weight of 10 g. for use at high levels of intra-ocular pressure. (Two-thirds actual size).

(*ii*) *Manometric Method.*—At the commencement of the work on intra-ocular pressure, of which the present investigation is a continuation, it was realized that continuous simultaneous blood pressure and intra-ocular pressure recordings were necessary if interpretation of intra-ocular pressure changes were to be reliable.

The apparatus at present in use has been evolved over the last 4 years, with assistance and advice from the technical staff of the Institute of Ophthalmology.

It consists of membrane manometers based on the design of Davson and Purvis (1950) so arranged that the image of a slit is reflected from mirrors mounted on the membranes and focused onto a running film, 120 mm. wide, contained in a specially constructed camera. Figs 6 and 7 show diagrams of one of the manometers.

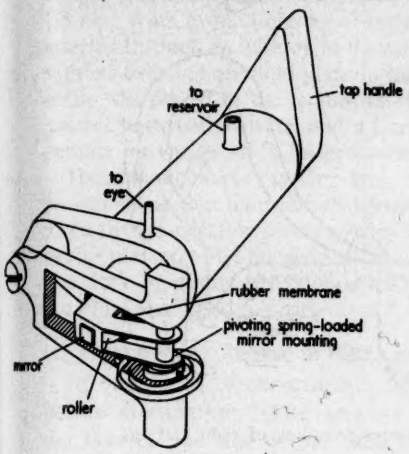


FIG. 6.—Diagram of membrane manometer and mirror mounting.

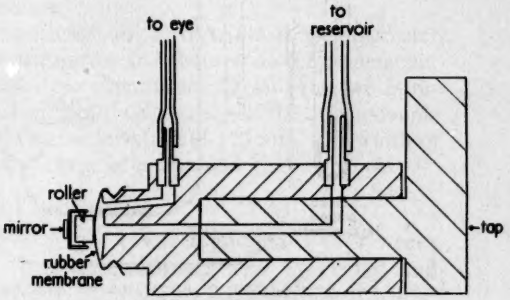


FIG. 7.—Section of membrane manometer.

Fig. 8 (overleaf) shows a diagram of the apparatus seen in the photograph (Fig. 9, overleaf).

The speed of the camera can be varied from 5 to 15 mm. per minute, this range having been found to be the most useful. A light flash at 1, 5, 10, 30 or 60 seconds acts as a time-marker on the film.

No attempt at accurate compensation to the pressure inside the eye is made, but the reservoir is raised to 25 cm. of saline and the saline allowed to flow from the needles during insertion into the anterior chamber. The pressure settles to a steady level in a few minutes and is rarely more than a few cm. above or below 25 cm. saline. Care is taken to reduce trauma to the minimum—a slight touch of the needle on to the iris is enough to cause a rise in intra-ocular pressure. This rise is accompanied by a contraction of the pupil (usually semi-dilated in the anaesthetized animal) and occurs within 5 minutes of the insertion of the needle. If, at the end of this period, the pressure is steady and the pupil dilated, recording is started and allowed to proceed for another 5 minutes before stimulation of the nerve under investigation. By this means it is reasonably certain that results are not influenced appreciably by the insertion of the needle.

The blood pressure is measured by means of a siliconed glass cannula inserted into the femoral artery and connected to a manometer of the same design as those used for recording intra-ocular pressure.

Details of the operative procedure involved will be described in the section on operative technique or in the descriptions of experiments. Electrical stimulation

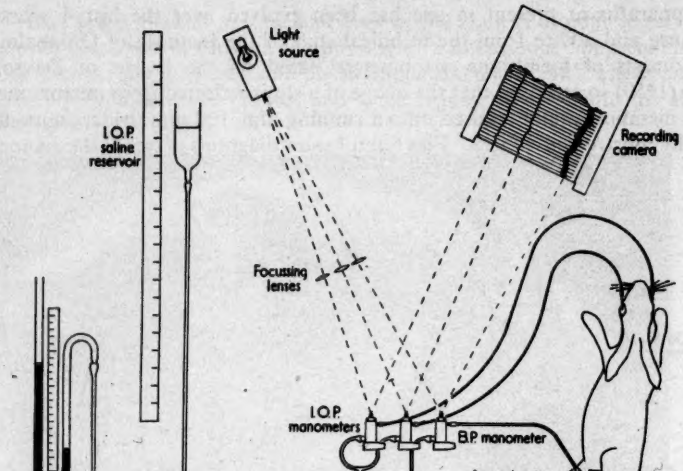


FIG. 8.—Diagram of apparatus for simultaneous recording of right and left intra-ocular pressure and blood pressure.

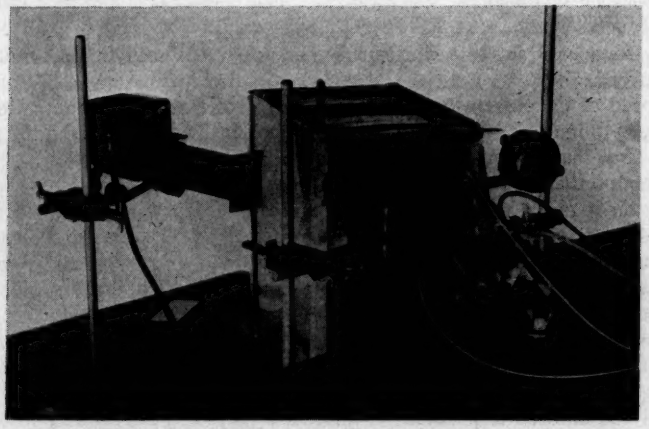


FIG. 9.—Photograph of manometers, illumination system, and camera.

of the nerves was provided by a square-wave electronic stimulator (Attree, 1950), and details of pulse width, frequency, and voltage will be given in the descriptions of the experiments.

For anaesthesia, urethane 1·75 g./kg. body weight in a dilution of 25 per cent. warmed to 37° C. and injected intravenously over a period of 4 to 8 minutes was used for experiments with rabbits, supplemented by the instillation of pantocaine

1·0 per cent. into the conjunctival sac before the insertion of the intra-ocular pressure needles.

(*iii*) *Temperature Measurements.*—The temperature of a tissue depends to a considerable extent on the rate of blood flow through it. In the eye it is possible to use temperature records to demonstrate changes in blood flow. A small copper-constantan thermocouple was made so that the junction protruded about 1·5 mm. from a small oblong of celluloid 2 × 4 mm. The junction could then be inserted through an incision in the sclera over the ciliary body and the conjunctiva sutured over the celluloid plate to hold it in position. Another thermocouple in series was placed in the rectum of the animal to compensate for changes in the general body temperature, and a third in series positioned near the head to compensate for variations in room temperature.

The thermocouple system was connected to a d'Arsonval galvanometer positioned so that light reflected from the mirror was focused on the camera slit. Thus the temperature changes were recorded simultaneously with the two intra-ocular pressures and the general blood pressure. Calibration of the thermocouple was done by means of a cooling curve, and a deviation of 120 mm. (the width of the film) was found to represent a 2° C. change of temperature.

(c) Operative Procedure in Survival Experiments

In one series of experiments the fifth nerve was sectioned 3 to 4 weeks before stimulation. The animals were anaesthetized with Pentothal and the skin of one side of the head shaved and cleaned with soap and water. Under sterile conditions, a specially-designed knife, similar to that used by Bernard (1858), was inserted through the cranial wall of the middle fossa and passed medially and slightly anteriorly until the pre-ganglionic part of the fifth nerve was touched, this being evident by a contraction of the pupil. The knife was now moved up and down to section the nerve. The ocular tension was measured before and after section of the nerve, using the applanation tonometer previously described.

The animals were watched carefully as the anaesthesia wore off, and the sensation of the lid and cornea tested by pricking the skin with forceps and touching the cornea. If these areas were anaesthetic the lids were sutured together to prevent corneal changes. Any animals showing signs of severe brain damage and haemorrhage were killed. Out of a total of 32 animals, 22 survived, and in fifteen of these satisfactory anaesthesia was obtained in the area supplied by the ophthalmic division of the fifth nerve.

(d) Histological

After the experiments on animals in which the fifth nerve had been sectioned previously, the rabbits were perfused by a cannula in the ascending aorta with 1 litre of a solution of magnesium sulphate 10 per cent. and potassium dichromate 2 to 3 per cent. The fifth nerves were then dissected out and stained by Marchi's method for degenerated fibres. The nerves were put into two parts 1 per cent. osmic acid and one part potassium dichromate and left for 3 days, when the solution was changed. Ten days

later the nerves were washed overnight in running water, then dehydrated through 70 per cent., 90 per cent., and absolute alcohol, and finally left in bergamot oil for 2 hours. They were then embedded in paraffin wax and sectioned.

On the advice of Dr. M. Smith, of the Hospital for Nervous Diseases, Queen Square, the changes seen in the sections stained by this method were confirmed in two other animals by a modified Marchi method and Glee's modification of Swank and Davenport's method.

Normal Anatomy of the Fifth Nerve in the Rabbit

Very little has been written in the literature concerning the anatomy of the fifth nerve in the rabbit. Bernard (1858) described the course of the nerve in the orbit as follows:

> The ophthalmic branch of the fifth nerve is distributed to the eye by three branches, the lacrimal, frontal, and nasal. The last branch gives fibres to the ciliary ganglion from which fibres go to supply the iris. Other fibres from the nasal branch enter the eye directly as the ciliary nerves.

Davis (1929) gives an excellent general description of the eye and orbit, and shows diagrammatically the course of the lacrimal and infra-orbital branches, but merely states in the text that the distribution of the nerve is similar to that in the human eye. The photographs and drawing shown here were made from dissections undertaken in the course of this work. It was found that dividing the head in a sagittal mid-line plane enabled the structures entering the orbital fissure to be exposed more easily than an approach *via* the middle fossa. The arrangement of the nerves entering and leaving the orbit is shown in Figs 10 and 11 (opposite).

Fig. 12 (opposite) shows a dissection in which the roof of the orbit has been removed, the recti muscles divided, and the globe retracted medially.

The general arrangement of the sensory nerves to the globe follows that of the human eye. Dissection of the branches of the ophthalmic nerve shows that there are three main branches of the nerve in the orbit, corresponding to the lacrimal, frontal, and naso-ciliary branches in man. These unite at the apex of the orbit and leave it through the superior orbital fissure in close company with the third, fourth, and sixth nerves. Branches can be traced from the rectus muscles and the ciliary ganglion which lies near to the optic nerve on its lower lateral aspect.

In the middle fossa, the ophthalmic division and the maxillary division (this latter being considerably larger) join and run backwards to the gasserian ganglion, which is an ill-defined swelling on the nerve, from whence a short root enters the pons. The third nerve lies above and medial to the combined trunk, the fourth above and laterally, and the sixth medially. The motor root joins the nerve at the ganglion.

Thus, in order to expose the preganglionic part of the nerve, a large part of the cerebral hemispheres has to be removed. It is possible to approach

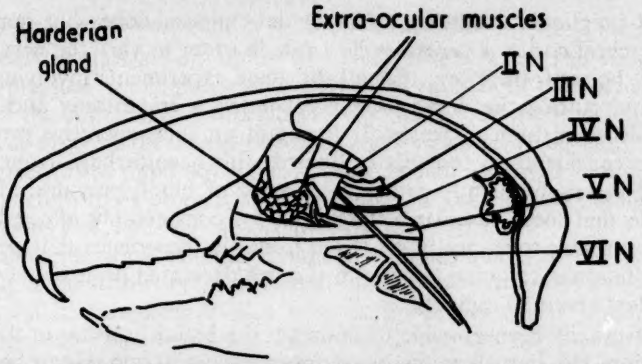


FIG. 10.—Diagram of cranial nerves seen after dissection of rabbit head divided in the sagittal plane.

FIG. 11.—Photograph of structures shown diagrammatically in Fig. 10.

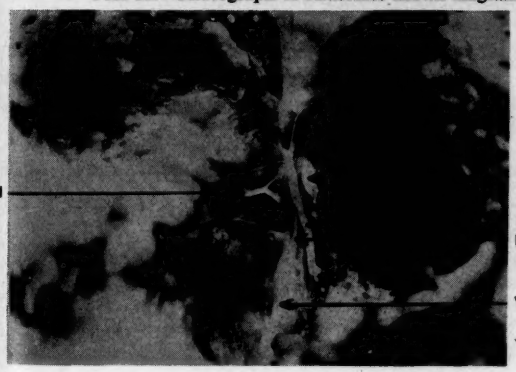


FIG. 12.—Photograph of dissection of structures entering rabbit's orbit. The globe has been rotated medially. Second, third, fourth, fifth, and sixth cranial nerves are indicated by arrows.

the post-ganglionic trunks by elevating the temporal lobes but removal of some cerebral cortex is necessary as a rule in order to view the nerve.

It will be seen, therefore, that all the acute experiments involving stimulating and cutting the nerve have necessitated a craniotomy and at least partial decerebration. The shock attendant on such operative procedures must be considerable, and this combined with haemorrhage from the cut cerebral vessels frequently causes a lowering of blood pressure. It seems probable that local vascular reflexes may be considerably affected by the general vascular tone, and it has been found by experience that peripheral vasodilatation in response to irritants is much decreased if the blood pressure falls below about 90 mm. Hg.

It has usually been possible to maintain the blood pressure in the region of 100 mm. Hg, but where the blood pressure was 90 mm. Hg or below, the results may not be significant and will be noted as such.

Experimental Results

I. Stimulation of the Intact Fifth Nerve

(1) Electrical Stimulation.—The nerve was exposed by craniotomy and partial decerebration, the femoral blood pressure cannula and intra-ocular pressure needles inserted, and the recording camera started. After 5 minutes, to allow the readings to become steady, a bipolar electrode was placed on the ophthalmic and maxillary trunk, and the nerve stimulated by a current of 5 volts at a frequency of 50 cycles per second for periods of 30 seconds to 2 minutes.

In two out of five animals, a rise in intra-ocular pressure on the side stimulated (7 cm. in one and 5 cm. in the other) followed the stimulation.

A possible reason for the difficulty in obtaining consistent results from electrical stimulation was found in another series of experiments, when fine glass electrodes were introduced into the nerve for purposes of recording action potentials. It was then found that the nerve sheath was very tough and fibrous, and offered considerable resistance even to electrodes as small as 5μ.

More powerful electric shocks might be more effective, but as other nerves are in close proximity, spread of impulse to them would be likely and difficult to control. Electrical stimulation was, therefore, abandoned and mechanical stimulation substituted.

(2) Mechanical Stimulation.—These experiments will be considered under the following headings:

(*a*) Effect on intra-ocular pressure
(*b*) Changes in episcleral vessels
(*c*) Changes in choroidal vessels
(*d*) Temperature changes in ciliary region
(*e*) Effect on permeability of blood–aqueous barrier
(*f*) Pupillary changes

(a) Effect on Intra-ocular Pressure

IPSILATERAL EYE.—In almost every experiment a marked rise in intra-ocular pressure in the ipsilateral eye followed rubbing of the post-ganglionic part of the fifth nerve. Mechanical stimulation of the intact nerve also caused a drop in the blood pressure, some movements of the rabbit and slight cries. The pupil always contracted immediately after stimulation and did not return to its original size for an hour or more. This pupillary effect is a curious one, and will be considered briefly later.

In man, and some animals, sympathetic fibres run with the ophthalmic division of the fifth nerve, and in order to eliminate any effects due to these fibres, stellate ganglionectomies were performed in twelve animals. The operation was done 4 or more weeks before the fifth nerve experiments to allow time for the sympathetic fibres to degenerate. This was not found to influence the changes in the ipsilateral eye, and even in those animals not previously sympathectomized, no dilatation of the pupil or vasoconstriction was noticed after stimulation of the fifth nerve. It seems likely, therefore, that the sympathetic fibres do not join the fifth nerve before it enters the orbit in the rabbit.

The sequence of events which follow mechanical stimulation of the fifth nerve is well shown in Fig. 13. The blood pressure shows an immediate drop which is reflected in a small fall in the intra-ocular pressure in both eyes. In the contralateral eye the pressure returns to its original level and remains at this level. In the eye on the side stimulated the pressure returns to its original level and continues to rise some 20 cm. saline. The rise is rapid and usually reaches its maximum in 5 minutes. The pressure then slowly declines during the following 30 minutes, in many cases never regaining its initial level.

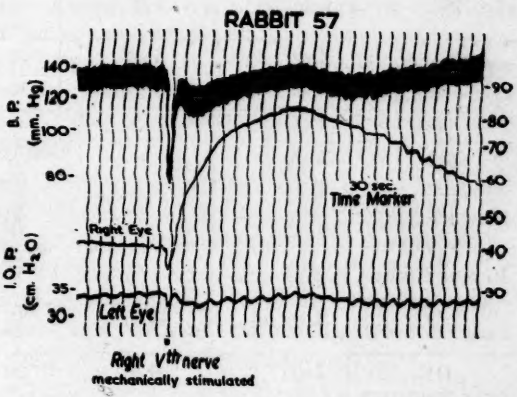


FIG. 13.—Recording of blood pressure and right and left intra-ocular pressures in a rabbit. Stimulation of the fifth nerve causes a sharp fall in blood pressure with rapid recovery which is reflected in a small fall in intra-ocular pressure in both eyes. The right intra-ocular pressure then commences to rise, reaching a maximum of over 80 cm. saline.

In Table III (overleaf) the arithmetical mean of the rise in pressure in the ipsilateral eye is 19·78 cm. saline.

TABLE III
INTRA-OCULAR PRESSURE CHANGES AFTER STIMULATION OF FIFTH NERVE

Rabbit No.	Side Stimulated	Side of Previous Sympathectomy	Rise in Intra-Ocular Pressure (cm. saline)	
			Ipsilateral Eye	*Contralateral Eye*
56	Right	—	12	No change
79	Left	—	6	No change
138	Right	—	No change	No change
235	Right	Right	20	No change
101	Right	Right	20	2
222	Left	Left	8	5
107	Left	Left	22	No change
266	Right	Left	25	25
57	Right (*a*) (*b*)	Left	22 25	4 No change
94	Right (*a*) (*b*)	Left	22 22	No change No change
144	Right	—	30	No change
14	Right (*a*) (*b*)	—	20 15	No change No change
144	Right (*a*) (*b*)	— —	25 20	5 No change
217	Right (*a*) (*b*)	— —	5 35	Not recorded Not recorded
240	Right	—	25	No change
126	Right	—	25	No change
209	Right (*a*) (*b*)	Left	7 No change	No change No change
211	Right	Left	40	5
84	Right	—	32	No change
69	Right	—	40	Not recorded
502	Right Left	— —	9 26	No change No change
192	Left Right	— —	Not recorded 35	No change No change
21	Left Right	— —	25 3	No change No change
39	Right (*a*) (*b*)	Left	10 5	No change No change
111	Right Left	Left Left	20 6	No change No change
202	Right (*a*) (*b*)	—	55 15	Not recorded Not recorded

CONTRALATERAL EYE.—In six out of 36 stimulations a rise in intra-ocular pressure occurred in the contralateral eye (Table III). The change did not occur immediately but took the form of a slow rise and fall, reaching a maximum about 15 minutes after stimulation. The height of the rise was usually about 5 cm. saline, but in one case it reached 25 cm. saline (Rabbit 266).

It would appear that previous sympathectomy on the contralateral side tends to facilitate a contralateral rise in intra-ocular pressure, as a higher proportion of contralateral rises, three out of seven stimulations, occurred in sympathectomized animals than in those with an intact sympathetic nervous system (Table III).

These contralateral changes will be discussed more fully at a later stage, but it is interesting to compare the type of tracing with those obtained after trauma to the eye. Here also contralateral changes, when they took place, were manifested by a slow rise and fall, reaching a maximum in some 15 to 30 minutes.

(*b*) *Changes in Episcleral Vessels.*—Rabbits anaesthetized with urethane were partly decerebrated to expose one fifth nerve. The episcleral vessels were then inspected, using a Zeiss binocular slit-lamp microscope.

The vessels were also photographed with a Kiné-Exacta camera, using an extension tube to give × 5 magnification. For the photographs illumination was provided by an electronic flash tube.

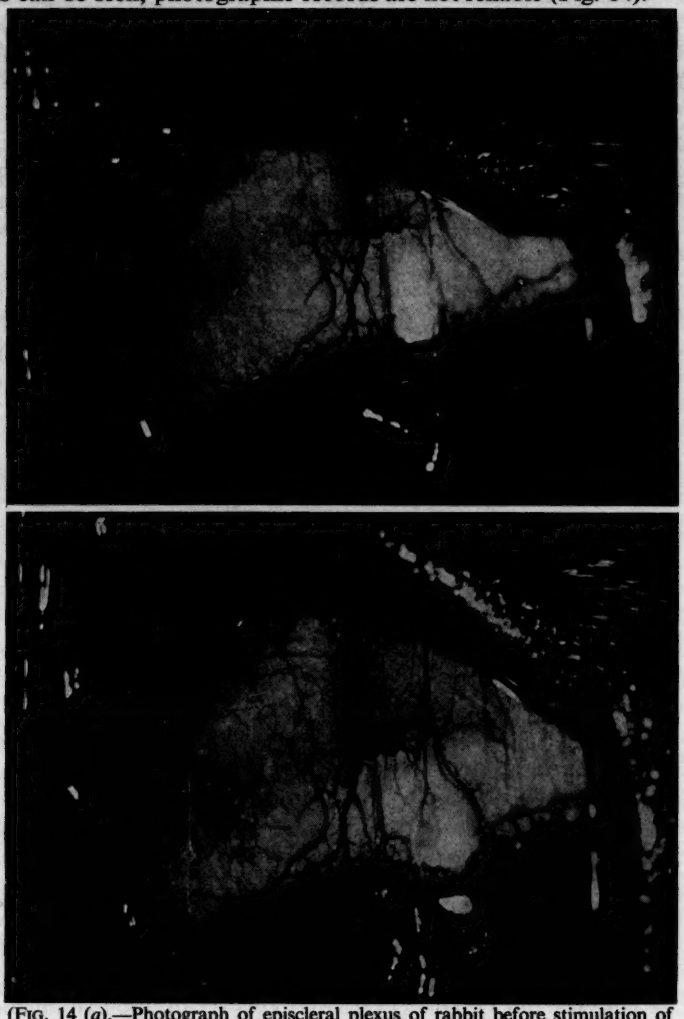
In order to keep the eye in position it was found necessary to insert a corneal suture and anchor this to the skin. The lids were also retracted by sutures.

One of the difficulties encountered in these observations on episcleral vessels was the dilatation of the vessels, due simply to exposure of the eye. Drying causes a definite vasodilatation, and in spite of precautions to keep the eye moist, the vessels were always more dilated after several observations had been made. Only the first few observations and photographs can, therefore, be considered significant.

On stimulation of the fifth nerve, the episcleral vessels appear to dilate within a minute or so, more vascular channels opening up with some slowing of the venous stream. Aqueous veins previously studied in the eye of the rabbit by Greaves and Perkins (1951) were observed during stimulation of the fifth nerve and were noticed to contain more blood than before stimulation. The changes mainly affect the capillaries and smaller arterioles and do not, therefore, show very clearly in the photographs.

The photographic appearances depend to a large extent on exposure time and development time of both negatives and prints. It is rarely possible to be absolutely sure that successive photographs will be of exactly the same

density, and unless a definite increase in calibre or increase in the number of vessels can be seen, photographic records are not reliable (Fig. 14).



(*a*)

(*b*)

FIG. 14 (*a*).—Photograph of episcleral plexus of rabbit before stimulation of fifth nerve. (×6·5).
FIG. 14 (*b*).—Photograph of same eye after stimulation of fifth nerve, showing vasodilatation of episcleral and conjunctival vessels. (×6·5.)

(*c*) *Changes in Choroidal Vessels.*—Albino rabbits anaesthetized with urethane were used for the experiments. As previously described, after craniotomy and partial decerebration, the choroid was then exposed.

Observations and photographs were then taken, the ipsilateral fifth nerve

was stimulated mechanically, and the choroid was again observed and photographed. No appreciable change in the calibre of the larger vessels was found to follow stimulation (Fig. 15).

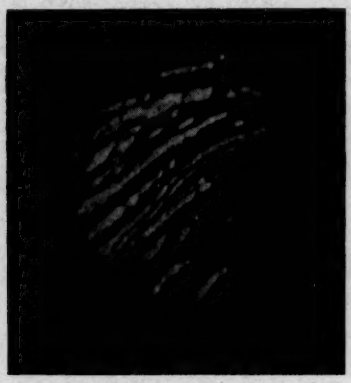


FIG. 15 (*a*).—Photograph of choroidal vessels of albino rabbit before stimulation of fifth nerve. (×13.)

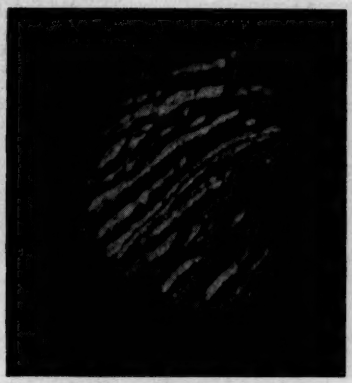


FIG. 15 (*b*). Photograph of same choroidal vessels after stimulation of fifth nerve. No appreciable change is seen in calibre of vessels. (×13.)

It is not possible to examine the capillaries in detail with this preparation, and any change taking place in them would not be noticed.

It is interesting in this connexion to note that Leopold (1951), in an extensive investigation of the action of drugs on the choroid using a scleral window technique, also found that the main choroidal vessels were not affected by a large variety of vasomotor drugs.

Our experiments on the sympathetic also failed to reveal changes in the main choroidal vessels, and from these results it seems likely that the choroid does not exhibit such vasomotor activity, except possibly in the capillary zone.

(*d*) *Temperature Changes in Ciliary Region*

IPSILATERAL EYE.—In every experiment except one, in which temperatures were recorded, stimulation of the fifth nerve was followed by an appreciable rise in the temperature (up to 1·5° C.) of the ciliary body on the same side (Table IV, overleaf). The rise started within a few seconds of stimulation and reached a peak some 5 minutes later; the later course varied. In some experiments a slow fall then followed, but only rarely did the temperature return to its initial value within the experimental period (approximately 1½ hrs). In other animals the temperature remained raised after stimulation.

It must be admitted that temperature readings taken by this method are open to error over prolonged periods. A small difference in the position of the thermocouple, such as may be brought about by the reflex movements of the animal after stimulation of the fifth nerve, could produce a change in base line. One would expect, however, that, if this was the explanation of

TABLE IV

TEMPERATURE CHANGES IN CILIARY REGION AFTER STIMULATION OF FIFTH NERVE

Rabbit No.	Side Stimulated	Side of Previous Ganglionectomy	Temperature Change (° C.)	
			Ipsilateral Eye	*Contralateral Eye*
242	Right	—	Rise 1·0	Not recorded
14	Right (*a*) (*b*)	— —	Rise 1·0 Rise 0·7	Not recorded Not recorded
144	Right (*a*) (*b*)	—	Rise 0·8 Rise 0·5	Not recorded Not recorded
217	Right (*a*) (*b*)	—	Rise 1·0 No change	Not recorded Not recorded
209	Right (*a*) (*b*)	Left	Not recorded Not recorded	Rise 1·5 Rise 1·5
211	Right	Left	Not recorded	Rise 0·5
84	Right	—	Rise 1·5	Not recorded
69	Right	—	Not recorded	Rise 1·0
202	Right Left	— —	Rise 0·2 Not recorded	Not recorded *No change
192	Left Right	—	Not recorded Rise 1·0	Rise 0·2 Not recorded
21	Left Right	—	Not recorded Rise 0·5	No change Not recorded
39	Right (*a*) (*b*)	Left	Not recorded Not recorded	Rise <0·1 Rise <0·1
111	Right Left	Left	Not recorded Rise 0·2	Rise <0·1 Not recorded
202	Right (*a*) (*b*)	—	Rise 0·3 Rise 0·3	Not recorded Not recorded

* Blood pressure below 90 mm. Hg after stimulation of right fifth nerve

the prolonged rises seen in some experiments, an equal number of animals would show a drop in the base-line reading. This has never occurred, and I think it is quite certain that a rise of temperature of the ciliary body is an invariable accompaniment of the fifth nerve stimulation.

CONTRALATERAL EYE.—The above experiments were repeated with stimulation of the contralateral intact fifth nerve in eight animals, and again a rise in temperature was obtained in six out of eight animals. The rise is not so marked in this eye, but it is quite definite and beyond experimental error (Table V, opposite).

It must be emphasized that, in these experiments, both fifth nerves were intact. The rise starts a few seconds after stimulation (Fig. 16, opposite).

TABLE V
SUMMARY OF CONTRALATERAL TEMPERATURE CHANGES

Rabbit No.	Side Stimulated	Side of Previous Ganglionectomy	Contralateral Temperature Change (° C.)
209	Right (*a*) (*b*)	Left	Rise 1·5 Rise 1·5
211	Right	Left	Rise 0·5
69	Right	—	Rise 1·0
202	Left	—	No change
192	Left	—	Rise 0·2
21	Left	—	No change
39	Right (*a*) (*b*)	Left	Rise 0·1 Rise 0·1
111	Right	Left	Rise 0·1

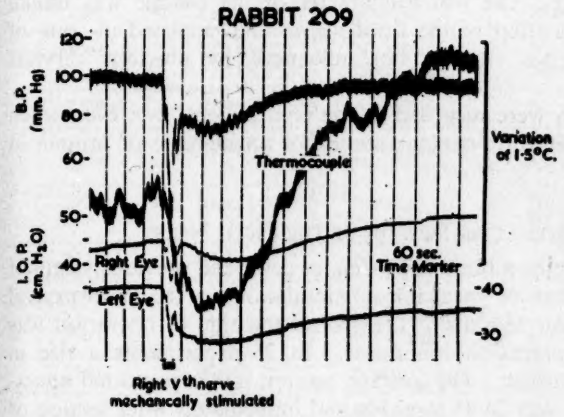


FIG. 16. — Recording of blood pressure, right and left intra-ocular pressures, and temperature of ciliary body of *left eye* after stimulation of *right eye*, showing contralateral rise in temperature without marked rises in intra-ocular pressure in either eye.

(*e*) *Effect on Permeability of Blood–Aqueous Barrier.*—At the end of experiments the aqueous humour was withdrawn from both eyes and tested for the presence of protein by adding an equal volume 5 per cent. trichloracetic acid.

In every case a thick precipitate of protein was obtained in the aqueous from eyes on the same side as the stimulated nerve. Frequently the aqueous was tinged with blood.

The findings in the aqueous of the contralateral eye were less consistent, but in twelve out of 24 experiments in which only one nerve was stimulated, a definite precipitate was obtained. In a few experiments there was almost as much protein present as in the other eye.

Slight amounts of protein are probably not significant, as this occasionally occurs following insertion of the needle for intra-ocular pressure measurement. However, a short series of experiments in which no intra-ocular pressure measurements were made, showed that the protein content of the aqueous was similarly increased, and it seems unlikely that any appreciable error is introduced by the method of measuring intra-ocular pressure with a needle in the anterior chamber.

It can, therefore, be concluded that stimulation of the fifth nerve always causes an increase in permeability of the intra-ocular vessels of the ipsilateral eye and may cause a similar though less intense change in the contralateral eye.

(*f*) *Pupillary Changes.*—In all experiments in which the intact fifth nerve was stimulated mechanically, a contraction of the pupil was observed on the side of stimulation. The contraction started a few seconds after the commencement of stimulation and progressed over the next 10 to 20 seconds, reaching a maximum about 30 seconds after stimulation. The miosis slowly decreased during the next 20 minutes but often lasted in some degree for more than an hour. The whole character of the change was unlike that produced by stimulation of the third nerve, and persisted in spite of atropinization of the eye. It was not influenced by previous cervical sympathectomy.

No pupillary changes were recorded in the contralateral eye, even when this eye showed a rise in intra-ocular pressure or an increase of protein in the aqueous.

II. Survival Experiments after Section of the Fifth Nerve

Cutting the fifth nerve by a blind approach, as described previously caused similar reactions to that of mechanical stimulation in the non-survival experiments. The ocular tension of the eye on the side of operation was measured with the applanation tonometer. In 25 experiments a rise in ocular tension was recorded. The average tension under pentothal anaesthesia before operation was 24·44 mm. Hg and immediately after section or attempted section the tension was 36·48 mm. Hg. The mean increase in pressure was 11·6 mm. Hg.

Section of the nerve always caused a marked contraction of the pupil to 2 to 3 mm. in diameter.

In ten of these survival animals the ocular tension of both eyes was measured under urethane anaesthesia 2 to 4 weeks after section. The average tension of the control eyes was 23·75 mm. Hg (S.E. 0·96, S.D. 3·04), and the average tension of the operated eyes was 22·70 (S.E. 0·87, S.D. 2·75), an average of 1·05 lower, but without statistical significance.

Two to 4 weeks after division of the nerve the animals were anaesthetized with urethane and decerebrated, and the fifth nerve was stimulated mechanic-

ally above and below the site of section. This experiment was performed successfully in eleven rabbits with the following results:

(1) Stimulation of the nerve on the cranial side of the section, either between the brain and the gasserian ganglion or between the ganglion and the site of section, caused a change in the size of the pupil in only one animal and this change was a small contraction of 0·5 mm. On only three occasions was a change in intra-ocular pressure recorded: in two cases a small rise of 5 cm. saline, and in one a rise of 3 cm. saline. Small contralateral rises in intra-ocular pressure were observed in two animals. A fall in blood pressure averaging 40·9 mm. Hg accompanied each stimulation (Table VI).

TABLE VI

INTRA-OCULAR PRESSURE CHANGES IN SURVIVAL EXPERIMENTS

Stimulation of Fifth Nerve ***Central*** *to Point of Section*

Rabbit No.	Side Stimulated	Intra-Ocular Pressure (cm. saline)		Fall in Blood Pressure (mm. Hg)
		Ipsilateral Eye	*Contralateral Eye*	
2094	Left	Rise 5	Rise 5	40
2098	Left (*a*)	No change	No change	50
	(*b*)	No change	No change	5
2225	Right	No change	No change	40
2132	Right (*a*)	No change	No change	40
	(*b*)	No change	No change	50
2220	Right (*a*)	No change	No change	30
	(*b*)	No change	No change	40
2221	Right	No change	No change	35
2297	Left	No change	No change	60
2367	Right	No change	No change	40
2366	Right	Rise 3	No change	50
2508	Right	Rise 5	Rise 3	50

Mean fall in blood pressure 42·3 mm. Hg.

(2) Stimulation of the nerve distal to the section caused a contraction of the pupil nine times out of eleven, the average change being 3·8 mm. The intra-ocular pressure showed a definite rise after all except one stimulation, the average rise being 18·4 cm. saline (Table VII, overleaf). A fall in blood pressure averaging 31·8 mm. Hg accompanied each stimulation, and on four occasions the contralateral eye showed a delayed rise in intra-ocular pressure of 2, 3, 7, and 13 cm. saline respectively.

Fig. 17 (overleaf) is a tracing from a typical experiment (Rabbit 2220).

The pupillary changes are shown in Tables VIII and IX (overleaf).

TABLE VII

INTRA-OCULAR PRESSURE CHANGES IN SURVIVAL EXPERIMENTS

Stimulation of Fifth Nerve ***Peripheral*** *to Point of Section*

Rabbit No.	Side Stimulated	Intra-Ocular Pressure (cm. saline)		Fall in Blood Pressure (mm. Hg)
		Ipsilateral Eye	*Contralateral Eye*	
230	Left (*a*) (*b*)	Rise 9 No change	No change No change	40 40
2094	Left	Rise 35	Rise 13	40
2098	Left	Rise 67	Rise 7	10
2225	Right	Rise 8	No change	40
2132	Right (*a*) (*b*)	Rise 8 Rise 5	Rise 2 Rise 3	40 50
2220	Right	Rise 13	No change	5
2221*	Right (*a*) (*b*)	No change No change	No change No change	30 30
2297	Left	Rise 35	No change	25
2367	Right	Rise 8	No change	30
2366	Right	Rise 15	No change	30
2508	Right	Rise 55	No change	50

Mean rise in intra-ocular pressure 18·4 cm. saline. Mean fall in blood pressure 32·8 mm. Hg.

* Subsequent examination of this animal showed that the fifth nerve had been sectioned at its point of entry into the orbit so that the peripheral portion could not be adequately stimulated from the middle fossa.

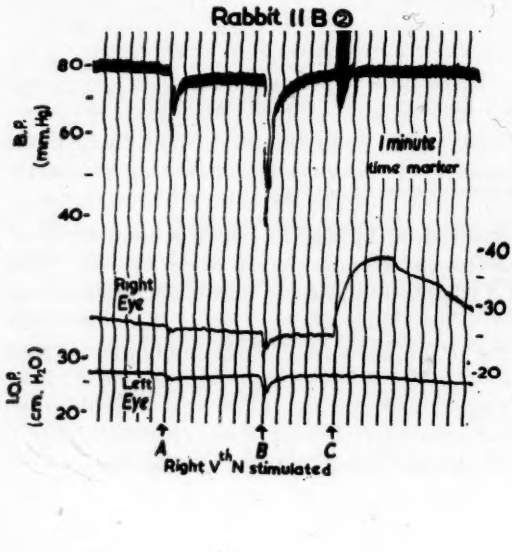


FIG. 17.—This animal had had the right fifth nerve cut 3 weeks previously.
(A) Stimulation of right fifth nerve between gasserian ganglion and brain; no rise in intra-ocular pressure.
(B) Stimulation of right fifth nerve between gasserian ganglion and point of previous section; no rise in intra-ocular pressure.
(C) Stimulation of peripheral cut end of nerve; rise in right intra-ocular pressure from 25 to 38 cm. saline.

TABLE VIII
PUPILLARY CHANGES IN SURVIVAL EXPERIMENTS
Stimulation of Fifth Nerve ***Central*** *to Point of Section*

Rabbit No.	Side Stimulated	Pupillary Contraction (mm.)	
		Ipsilateral Eye	*Contralateral Eye*
2094	Left	No change	No change
2098	Left (*a*) (*b*)	No change 0·5 contraction	No change No change
2225	Right	No change	No change
2132	Right (*a*) (*b*)	No change No change	No change No change
2220	Right (*a*) (*b*)	No change No change	No change No change
2221	Right	No change	No change
2297	Left	No change	No change
2367	Right	No change	No change
2366	Right	No change	No change
2508	Right	No change	No change

(*a*) and (*b*) indicate two separate stimulations

There are two possible explanations for these blood pressure and contralateral intra-ocular pressure changes; either, in stimulating the peripheral portion, the central end of the nerve was also stimulated, or the maxillary division of the trigeminal nerve, which lies beneath and in contact with the ophthalmic division, was stimulated. The latter supposition could certainly account for the blood pressure changes.

The surprising results on the pupil and intra-ocular pressure after stimulation of the peripheral part of the nerve indicated that, although the nerve had been completely divided, as shown by the anaesthesia in its area of distribution, some fibres were still active. The only explanation seemed to be that ganglion cells were present peripheral to the point of section. If this were the case, histological examination of the nerve *central* to the section should show degenerated fibres. The presence of undegenerated fibres in the peripheral part of the nerve would not be conclusive evidence as it could be interpreted as due to incomplete section. In the later animals, therefore, the nerve was dissected out after the completion of the experiment and examined histologically, with the results detailed below.

III. Histological Results

In eleven experiments, the fifth nerves from both sides were removed, stained by Marchi's method, and sectioned. In every case degenerated

TABLE IX
PUPILLARY CHANGES IN SURVIVAL EXPERIMENTS
Stimulation of Fifth Nerve ***Peripheral*** *to Point of Section*

Rabbit No.	Side Stimulated	Pupillary Contraction (mm.)	
		Ipsilateral Eye	*Contralateral Eye*
203	Left (*a*)	1·0 contraction	No change
	(*b*)	0·5 contraction	No change
2094	Left	5·0 contraction	No change
2225	Right	5·0 contraction	No change
2098	Left	6·5 contraction	No change
2132	Right (*a*)	2·0 contraction	No change
	(*b*)	1·0 contraction	No change
2220	Right	4·0 contraction	No change
2221*	Right	No change	No change
2297	Left	4·0 contraction	No change
2367	Right	1·5 contraction	No change
2366	Right	No change	No change
2508	Right	4·0 contraction	No change

Mean pupillary contraction 2·7 mm.

* This animal also showed no changes in intra-ocular pressure. (See note under Table VII).

fibres were found in the nerve which had been cut some weeks previously. A study of these preparations revealed, however, that ganglion cells extended much further into the periphery of the nerve than had been anticipated, and in two longitudinal series of sections the gasserian ganglion was shown to be a rather diffuse structure extending over 1 cm. of the nerve. In these sections there were a few ganglion cells in the region of the cut end of the nerve, and it seemed very possible that the results obtained from stimulating the peripheral nerve outlined above could be explained by the presence of ganglia in this part of the nerve.

In order to be sure that ganglion cells were not present within the globe, one eye was enucleated or eviscerated (two animals) and the fifth nerves examined for degeneration. No degeneration was found, and evisceration of the socket in one further animal also failed to reveal degeneration in the fifth nerve trunk.

Discussion

The effects on the intra-ocular pressure obtained in the stimulation experiments on the intact fifth nerve confirm the findings of many of the older workers on rabbits and dogs (Magendie, 1824; Bernard, 1858; Donders, 1864; von Hippel and Grünhagen, 1868; von Schultén, 1884; Vulpian, 1885; Bellarminoff, 1886).

It is strange that these effects should not have been further investigated since the turn of the 19th century, but it seems likely that the results in the cat of Henderson and Starling (1904), in which they showed that the rise in intra-ocular pressure was due only to stimulation of the sympathetic fibres, cast so much doubt on the validity of the previous results that the subject was not pursued. This failure to explore the matter persisted in spite of the continued interest in the effects on the intra-ocular pressure of contusion and injury to the eye, in which the sensory nerves were likely to play a large part. The contraction of the pupil after stimulation of the nerve was likewise neglected since the time of Bernard (1858), until Maurice (1954) found that antidromic stimulation of the fifth nerve caused contraction of the pupil in rabbits even after previous sympathetic denervation of the eye. Maurice reported that, when the pupil had recovered from section of the fifth nerve, it contracted again on stimulation of the peripheral stump but not of the central stump. If the fifth nerve were allowed to degenerate after section distal to the gasserian ganglion, this pupillomotor effect could not be obtained, though dilatation occurred normally on sympathetic stimulation. He also noted that a contraction could be obtained some minutes after the animal had been killed by exsanguination, and that exsanguination had no influence on the size of a pupil already contracted. He concluded that this showed that the effect did not result from liberation of a pupillomotor substance into the blood stream, and was unlikely to be due to a vasomotor action on the vessels of the iris.

The experiments described in this thesis substantiate the findings of Maurice, although some degree of pupillary contraction was obtained in most of the survival experiments when the peripheral portion of the nerve was stimulated. It is probable that, in the experiments performed by Maurice, the nerve was divided more peripherally, leaving fewer or no ganglion cells in the peripheral nerve trunk.

Although this work has been concerned primarily with intra-ocular pressure changes, it is interesting to consider what factors may be involved in the contraction of the pupil which follows stimulation of the fifth nerve. The theoretical possibilities are as follows:

(*a*) Accidental stimulation of the third nerve.
(*b*) A reflex arc with the fifth nerve as the sensory limb and the third nerve as motor part.
(*c*) Intense vasodilatation of the blood vessels of the iris causing a mechanical miosis.
(*d*) Inhibition of sympathetic tone.
(*e*) The liberation of some substance at the fifth nerve endings which causes contraction of the sphincter pupillae.

(*a*) *Accidental Stimulation of the Third Nerve.*—When the experiment was performed in decerebrated animals, it was possible to see the third and fifth nerves and to be quite sure that the third nerve was not touched. The

character of the contraction is also unlike that which follows stimulation of the third nerve, being slower in onset and persisting much longer after stimulation has ceased.

(*b*) *A Reflex Arc.*—This possibility can be eliminated for two reasons. First, in the experiments in which the fifth nerve had been divided previously, stimulation of the central part of the nerve did not cause a contraction of the pupil. Secondly, stimulation of the intact nerve caused a contraction of the pupil after the third nerve had been sectioned.

(*c*) *Vasodilatation.*—Congestion of the blood vessels of the iris is known to cause some degree of miosis, as for example in acute iritis. However, Maurice has shown that the effect persists after exsanguination of the animal, so that it cannot be due to vasodilatation only.

(*d*) *Inhibition of Sympathetic Tone.*—Division of the sympathetic supply to the pupil caused only a slight degree of miosis in the rabbit, and previous cervical sympathectomy did not affect the pupillary contraction after fifth nerve stimulation.

(*e*) *Liberation of an Active Substance.*—This final possibility seems to be the most likely explanation, and has received considerable support from the work of Ambache (1956). He has tested extracts of rabbit iris and fifth nerve on preparations of rat colon and has found evidence of an active substance "Irin", which can be differentiated from all the known substances of this type so far investigated, especially those obtained from extracts of muscle and nerve. This substance has also been found to contract the pupil in the rabbit, and it seems likely that this is the substance which is released by stimulation of the fifth nerve.

Although vascular changes have been found to occur in the contralateral eye, in no experiment was a contraction of the pupil noted in the contralateral eye. Bernard (1858), who sectioned (thereby stimulating mechanically) the fifth nerve in conscious animals, noticed contraction of the pupil on the ipsilateral side, but did not report any contralateral pupillary changes. It is unlikely, therefore, that the failure to observe such changes in the experiments reported here was due to the use of general anaesthesia. It is probable that the vascular and pupillary changes are brought about by separate mechanisms, one of which acts only on the side of stimulation, while the other can affect both eyes.

Changes in Ocular Vessels and Intra-Ocular Pressure

Cutting the fifth nerve has the same immediate effects as mechanical stimulation. In animals which were allowed to recover, the intra-ocular pressure on the side of operation tended to be slightly lower 3 or 4 weeks after the operation, but the results were not statistically significant. In these animals the pupils were equal.

In considering the cause of the rise of intra-ocular pressure produced by stimulation of the fifth nerve, it is easiest to enumerate all the factors which may cause a rise in intra-ocular pressure and apply the experimental evidence to each factor in turn.

(1) *External pressure on the globe from contraction of smooth muscle or extra-ocular muscles.*

This factor can be excluded, as no eye movement or lid movement occurs.

(2) *Increase in blood volume within the globe.*

There is definite evidence that a vasodilatation does occur on stimulating the fifth nerve and it is very likely that the rapid rise in pressure is due in part to this factor.

(3) *Increased formation of aqueous.*

These experiments give no direct evidence of an increased formation of aqueous, but the vasodilatation would be expected to have this effect.

(4) *Change in osmotic pressure of the aqueous humour.*

Aqueous humour normally contains little protein, but after stimulation of the fifth nerve the permeability of the blood-aqueous barrier increases and allows much protein, and even sometimes blood corpuscles, to enter the anterior chamber. Thus the osmotic pressure of the fluid in the anterior chamber will be much increased, contributing to the rise in pressure.

(5) *Obstruction of the outflow channels.*

The large amounts of protein in the aqueous must tend to block the angle, and occasionally the manometer needle becomes blocked completely. It is likely, therefore, that this is a factor of some importance.

(6) *Increased episcleral venous pressure.*

The aqueous veins have been observed to be filled with blood after stimulation of the fifth nerve, but although this could be due to an increase in episcleral venous pressure it could also be due to a lower pressure in the aqueous veins themselves. As direct measurements of episcleral venous pressure are unsatisfactory in the rabbit, the importance or otherwise of this factor is difficult to assess.

Contralateral Effects

The changes in the contralateral eye which follow stimulation of one fifth nerve are particularly interesting. It seemed at first, when a rise in intra-ocular pressure was used as the criterion, that contralateral effects occurred relatively infrequently—six times in 36 experiments—but, when the aqueous humour of the eyes was examined for protein, appreciable amounts were found in half the contralateral eyes. The more refined technique of

temperature recordings from the ciliary region also showed that some contralateral effect followed the stimulation in six out of eight experiments.

It is, therefore, very likely that stimulation of one fifth nerve produced a vasodilatation in the contralateral eye in a high proportion of cases, and that this vasodilatation was followed by an increase in permeability in half the animals, but in only 15 per cent. of such stimulations were these changes sufficiently marked to cause a rise in intra-ocular pressure. This figure is comparable to the number of rises in the intra-ocular pressure in the contralateral eye found in experiments involving a contusion injury to one eye (Table II).

There are three possible explanations of these contralateral changes:

(1) That it is a non-specific result of the rather severe shock which follows stimulation of a sensory cranial nerve. The large fall in general blood pressure which always accompanies stimulation of the fifth nerve could cause peripheral vascular constriction, and on recovery of the blood pressure a reactionary vasodilatation of ocular vessels might take place.

There is a little corroborative evidence for this suggestion from some experiments in which a T cannula was tied into the common carotid. It was found that, if total occlusion of the common carotid lasted for more than 2 minutes, release of the occlusion was sometimes followed by a rise in intra-ocular pressure on the side of the occlusion. However, the fall in blood pressure after stimulation of the fifth nerve rarely lasts longer than half a minute, and it seems unlikely that this in itself would be sufficient to account for the contralateral effect.

(2) That after stimulation of the fifth nerve a vasodilator substance is released into the blood stream and reaches the contralateral eye. This implies a substance whose action is limited to ocular vessels and is not destroyed in the blood stream. There is no evidence for such a substance. " Irin ", which is probably responsible for the pupillary contraction, has, so far as is known at present, no vasodilator action and certainly does not reach the opposite eye in sufficient concentration to cause a contraction of the pupil.

(3) That a stimulus reaches the contralateral eye *via* a nervous pathway. The sympathetic system can be excluded as contralateral changes occurred after the sympathetic supply to the eye had been removed.

A direct pathway up the stimulated nerve to its nucleus in the brain, crossing to the opposite nucleus and descending antidromically in the opposite fifth nerve seems the most likely explanation of the contralateral changes. The evidence in favour of this explanation is as follows:

(*i*) The type of change—vasodilatation followed by increased permeability —is the same in the contralateral eye as in the eye on the side of stimulation, though less in degree.

(*ii*) The vasodilatation, as shown by the temperature recordings, occurs at about the same time interval after stimulation in both eyes.

(*iii*) The association between depth of anaesthesia and the frequency of the contralateral changes suggests a nervous pathway. In this connexion it is interesting that Leplat (1924) found contralateral changes more frequently in unanaesthetized than in anaesthetized animals.

(*iv*) Perhaps the most conclusive evidence derives from seven experiments in which an intact nerve on one side was stimulated after cutting the nerve on the contralateral side; no intra-ocular pressure rise was noticed in the contralateral eye. In one of these experiments, temperature recordings were taken from the ciliary region of the contralateral eye and showed no change after stimulation.

The vasomotor changes which follow stimulation of the fifth nerve conform to the pattern previously noted in peripheral sensory nerves. It seems likely that these changes are connected in some way with the axon reflex which is also mediated by sensory nerves. Duke-Elder and Duke-Elder (1931) showed that an axon reflex can be elicited from the rabbit iris, and presumably an antidromic stimulus applied to the fifth nerve could be conducted along that part of the axon reflex pathway which terminates in relation to the capillaries of the eye and could produce a vasodilatation similar in character to that invoked by an axon reflex.

The survival experiments and the histological results have shown that ganglion cells extend peripherally in the ophthalmic branch of the fifth nerve in rabbits. As no degenerative changes were found in the nerve after enucleation of the eye and evisceration of the orbit, the ganglion cells must be confined to the main trunk of the nerve.

From the more general viewpoint of the nervous control of intra-ocular pressure, these experiments show that the fifth cranial nerve in rabbits can mediate impulses for raising the intra-ocular pressure. This does not necessarily imply that the nerve takes an active part in the normal control of intra-ocular pressure; the fact that animals in which the nerve had been divided some weeks previously showed little change in ocular tension is against such a suggestion, but does not exclude the possibility. It may well be that the intra-ocular pressure is to some extent self-regulatory under normal conditions, and that the nervous mechanisms are only brought into action when the equilibrium is disturbed.

Under pathological conditions, however, it is probable that local irritative lesions in the eye stimulate the fifth nerve endings, cause reflex vasodilatation, and raise the intra-ocular pressure. Lesions which stimulate the trunk of the ophthalmic division or the gasserian ganglion might also cause similar changes, and it may be of some significance that glaucoma following herpes zoster ophthalmicus in the absence of an anterior uveitis has been reported in man (Salomaa, 1951). It must be emphasized, however, that the results of

experiments performed on rabbits cannot be applied unreservedly to the human eye.

Summary of Results

(1) Mechanical stimulation of the intact fifth nerve caused, on the side of the stimulation, a contraction of the pupil, a rise in temperature of the ciliary region, a rise in intra-ocular pressure, and an increase of protein in the aqueous humour.

(2) In the contralateral eye, no contraction of the pupil resulted from stimulation of the opposite intact fifth nerve, but a rise in intra-ocular pressure occurred in 15 per cent. of animals. In half the experiments an increase in protein was found in the aqueous humour of the contralateral eye, and in six out of eight animals a rise in temperature of the ciliary region was recorded.

(3) Section of the fifth nerve produced the same immediate effects as stimulation. Although the tension of the eye on the side of section tended to be slightly lower than that on the normal side when measured 2 to 4 weeks later, the differences were not statistically significant.

(4) Stimulation of the fifth nerve caused a vasodilatation of the episcleral vessels of the ipsilateral eye. No change was found in the choroidal vessels of this eye.

(5) In animals in which the fifth nerve had been sectioned 2 to 4 weeks previously, stimulation of the cranial portion of the nerve caused no changes in the pupil or intra-ocular pressure.

(6) Histological examination of the nerves previously sectioned showed degenerated fibres in that part of the nerve central to the section. These fibres probably arose from ganglion cells in the trunk of the fifth nerve peripheral to the point of section.

(7) It is concluded that the vascular changes in the eye which follow antidromic stimulation of its sensory nerve supply are comparable to the vascular changes in the skin which follow antidromic stimulation of the peripheral sensory nerves.

I wish to acknowledge most gratefully the constant help and advice received in the course of this work and the preparation of this paper from Sir Stewart Duke-Elder, Director of Research, Institute of Ophthalmology.

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CORNEO-SCLERAL TONOGRAPHY*†

BY

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THAT pressure exerted on the eyeball caused a lowering of ocular tension has been known for many years (Pagenstecher, 1878; Schiötz, 1908; Thomassen, 1946). However, it was not until the introduction of the electronic tonometer and the subsequent work of Grant (1950, 1951) that the knowledge thus gained could be translated into an easily measured form which has gained wide clinical acceptance.

In all this work bulbar pressure has been exerted either on the cornea or on the sclera, and the results variously interpreted. Blaxter (1953) reported on a large number of cases in which simultaneous pressure lasting 4 minutes was applied to the cornea by a Schiötz X tonometer and to the sclera by a Bailliart dynamometer. Our present investigation has combined both corneal and scleral compression, using the Mueller electronic tonometer in a method which is easily standardized and causes a minimum of discomfort to the patient, and which, we believe, yields valuable information, particularly with regard to border-line cases.

Method

The patient is placed in the supine position. Care is taken to ensure that there is no constriction by neck bands. A marker on the ceiling directly overhead and a marker on the wall to the right and to the left are pointed out to the patient. The two side markers are so located that when, for example, the left eye is fixing on the spot to the right, enough bulbar conjunctiva is exposed temporal to the cornea to accommodate the foot-plate of the tonometer with 2 mm. of conjunctiva still separating the tonometer from the limbus (Fig. 1).

FIG. 1.—Bulbar conjunctiva exposed to receive tonometer.

A drop of 0·5 per cent. pantocaine is instilled into each eye. The patient is first instructed to fix on the overhead marker and the electronic tonometer is applied to the cornea, the lids being separated by the operator. All readings are

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† Assisted by a Federal Health Grant.

recorded on a Sanborn recorder. After a 15-second interval, if the left eye is being tested, the patient is instructed to transfer fixation to the spot on the wall to the right.

The tonometer is now re-applied over the temporal conjunctiva leaving 2 mm. of free conjunctiva between the foot-plate and the limbus (Fig. 2). This position is held for exactly 3·75 minutes. At the end of this period the tonometer is re-applied to the cornea with the eye in the original position (looking at the ceiling) for a final 15-second recording.

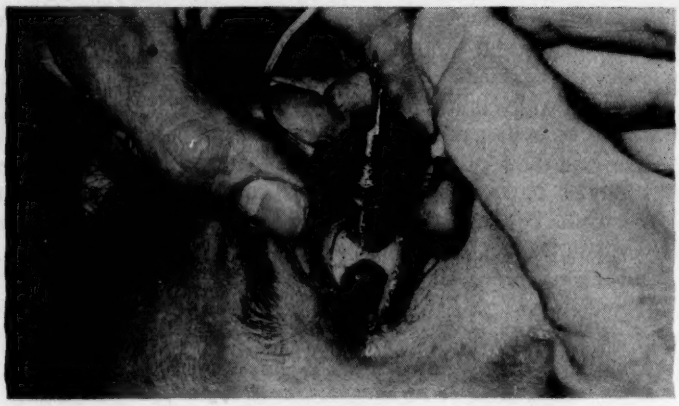


FIG. 2.—Electronic tonometer in position.

All timing is done accurately by stop watch and plotted on a graph by the assistant. The watch is always stopped during transfer of fixation and re-started on re-application of the tonometer. This transfer period may take from 1 to 3 seconds, during which time the patient may blink to moisten the cornea. The greatest care must be exercised at all times to avoid tension on the lids.

In cases of irregular readings, corneal tonography may be continued slightly longer before and after scleral compression. A mean curve drawn over the plotted points can then be extrapolated forward and backward respectively to the edge of the scleral compression period.

The mean reading at the end of the corneal tonography, just before scleral compression, is taken as the initial reading, and the reading after scleral compression, at the end of the final 15-second period of corneal tonography, is taken as the final reading. Thus a period of compression of exactly 4 minutes, the final 15 seconds of which was corneal, has been measured.

In our series corneal tonography was done on all cases for comparative purposes.

Results

The results of corneal tonography and the results of corneo-scleral tonography as outlined in our method both demonstrated a lowering effect on the intra-ocular pressure. In Figs 3 and 4 (opposite) the initial reading is plotted against the final reading. With both methods tonography showed a generally greater lowering effect in normal eyes than in glaucomatous eyes.

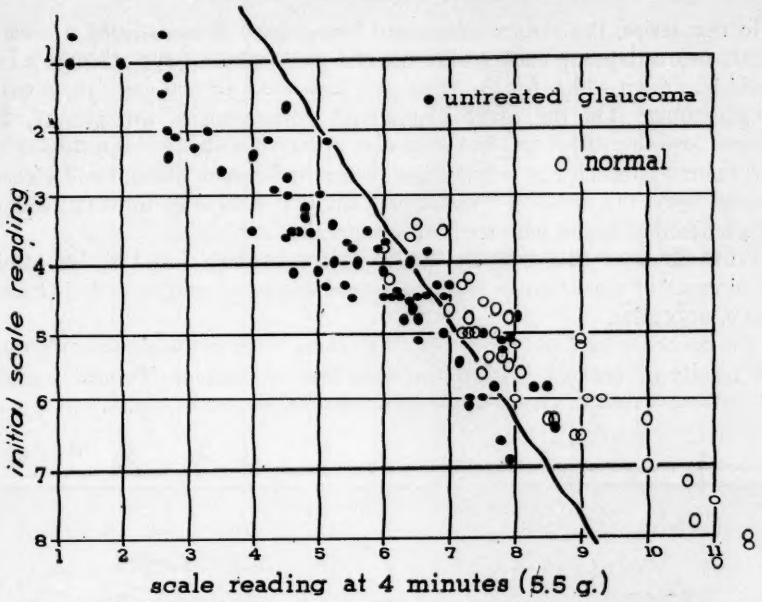


FIG. 3.—Distribution of results of corneal tonography, showing border-line between normal and glaucomatous eyes.

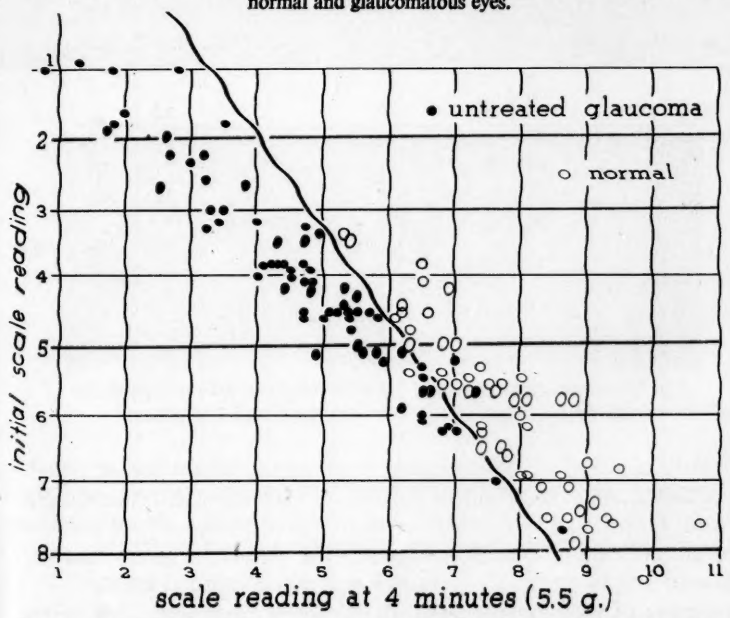
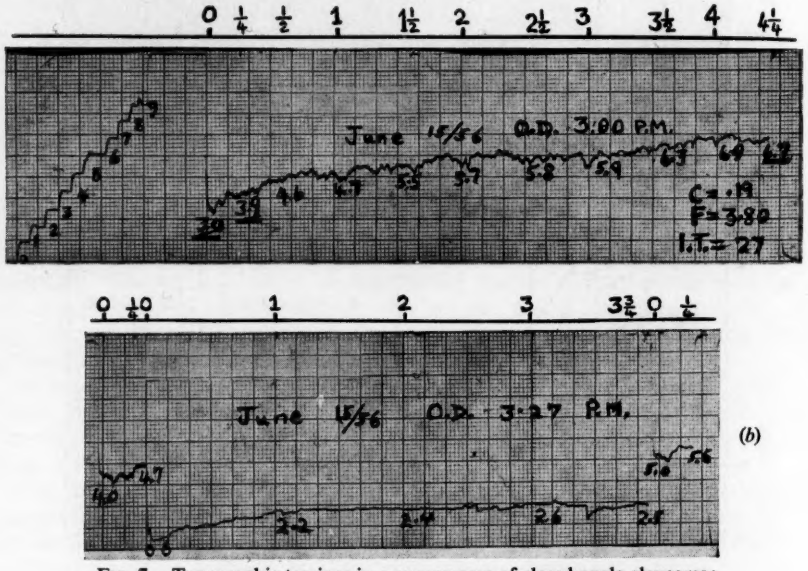


FIG. 4.—Distribution of results of corneo-scleral tonography, showing border-line between normal and glaucomatous eyes.

In our series, the results of corneal tonography demonstrated a certain degree of overlapping between normal and glaucomatous eyes, though a line could be drawn which for the most past separated normal cases from cases of glaucoma. On the other hand, with corneo-scleral tonography, the general lowering effect was less than that observed with corneal tonography, and there was much less overlapping of results between normal and glaucomatous eyes; the dividing line between the two groups is, however, almost parallel to that found with corneal tonography.

From the cases shown in the preceding graphs (Figs 3 and 4), the results of all cases of closed-angle glaucoma were extracted and recorded (Figs 5 and 6, opposite).

The corneo-scleral technique placed all these cases in the glaucoma group; the results of corneal tonography were less conclusive. Typical tracings taken from a case of closed-angle glaucoma are shown in Fig. 7.



(a)

(b)

FIG. 7.—Tonographic tracings in a proven case of closed-angle glaucoma:
(*a*) Corneal method; (*b*) Corneo-scleral method.

Similarly, a group of cases showing moderate to severe loss of visual field were extracted, and the results of corneal and corneo-scleral tonography are shown in Figs 8 and 9 (overleaf). Here again corneo-scleral tonography placed all, even the low tension cases, in the glaucoma group, but corneal tonography placed some of these cases well within normal limits.

Two cases of pseudoglaucoma, not shown in the graphs, fell within the normal group with both methods of testing.

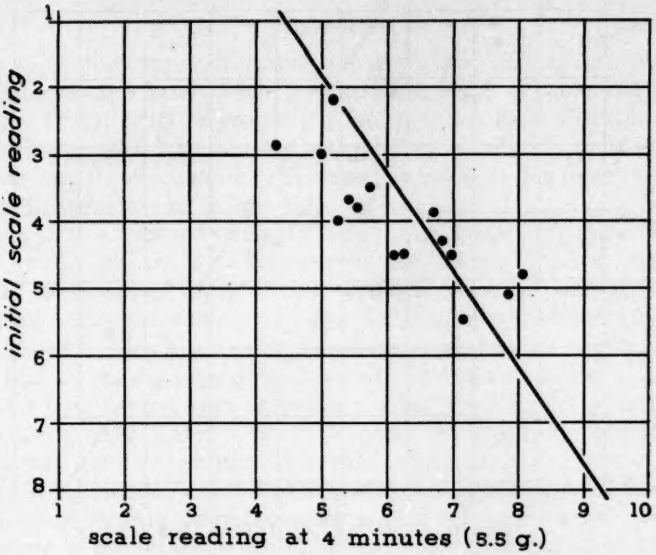


FIG. 5.—Distribution of results of corneal tonography in closed-angle glaucoma.

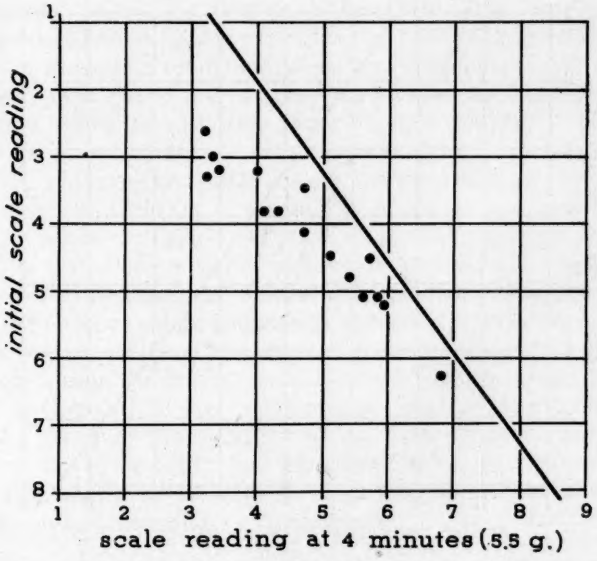


FIG. 6.—Distribution of results of corneo-scleral tonography in closed-angle glaucoma.

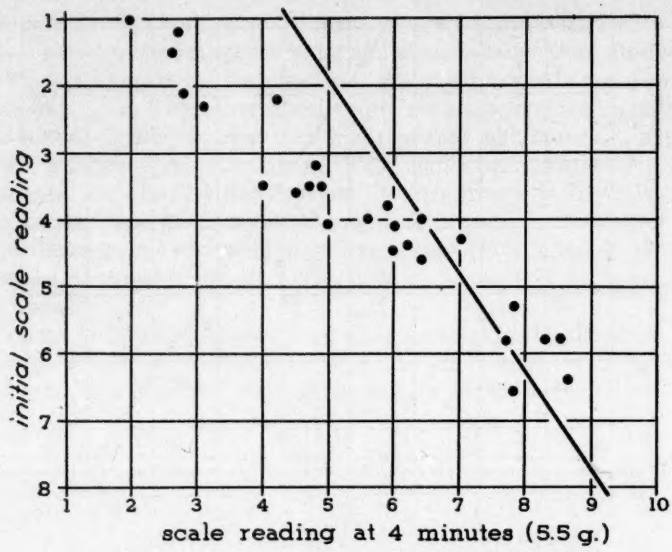


FIG. 8.—Distribution of results of corneal tonography in cases of moderate to severe loss of visual field.

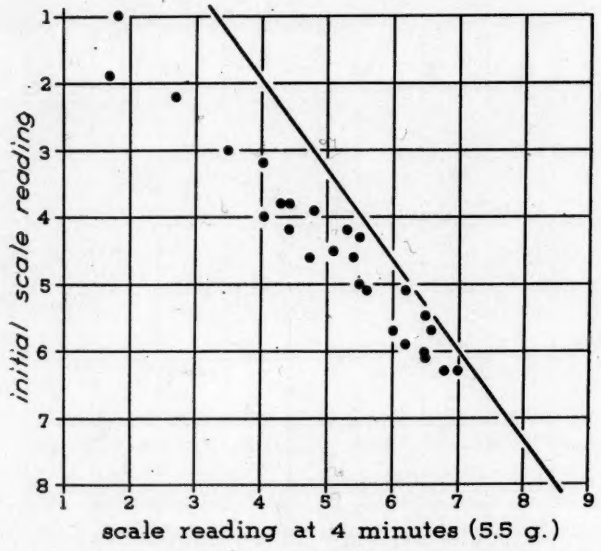


FIG. 9.—Distribution of results of corneo-scleral tonography in cases of moderate to severe loss of visual field.

Discussion

The slight discrepancy in the location of the dividing line between normal and glaucomatous cases which is seen in this series as compared with that of Grant (1950, 1951), is probably as much as would be found in any two centres doing carefully controlled tonography. Obviously, each laboratory must develop its own criterion of border-line cases, having in mind the slight inevitable differences of technique and apparatus.

That the 1 to 3 second interval allowed for transfer of fixation in corneo-scleral tonography made no difference to the test can be demonstrated with corneal tonography. Here, if the tonometer is lifted and replaced, no significant difference will be found in the tension before and after such a short interval. It is again pointed out, however, that the assistant stopped the watch for the duration of the interval, short though it was.

That scleral compression generally resulted in as lighter lowering effect than corneal compression is felt to be partly the result of encroachment of the iris root on the angle structures with subsequent impairment of outflow. This encroachment of iris root may result from forward displacement of the vitreous body or from secondary engorgement of ciliary vessels. Whichever is the case, a certain degree of compression of angle structures and subsequent embarrassment to aqueous filtration is likely to take place. Interference with the more superficial collector channels, whether carrying aqueous humour or blood, by direct pressure of the tonometer foot-plate must also be considered. On a purely physical basis, this area compressed by the tonometer could not influence more than one-tenth of the available channels. Because corneo-scleral tonography does not bring normal eyes with narrow angles within the glaucomatous group, the forward displacement of vitreous alone could not be the sole cause of the impaired outflow.

The results in closed-angle glaucoma are thought to indicate not the severity of the disease but rather the susceptibility to angle embarrassment.

Why cases of moderate to severe loss of visual field, even those from among the low tension glaucoma cases, should fall within the glaucomatous group after scleral compression, rather than after corneal compression is a more intriguing observation. Ease of compressibility of somewhat tenuous venous and aqueous escape channels is a possible explanation.

As a corollary we tested two cases of glaucoma which had shown a constant high tension for several years, not responding too well to treatment but not developing field loss or symptoms. Both of these cases came well within the glaucomatous group when tested by corneal compression, but came very close to the border-line when tested by scleral compression. Thus it seems that, apart from closed-angle cases, the results of scleral compression give some idea of the severity of the disease.

Summary

(1) Corneo-scleral tonography using the electronic tonometer is a practical and fairly accurate test in the diagnosis of glaucoma.

(2) Cases of closed-angle glaucoma, even in interval stages, fall within the glaucomatous group.

(3) Cases of moderate to severe loss of visual field, even in true low pressure glaucoma, fall within the glaucomatous group.

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EXPERIMENTAL DEGENERATION OF THE RETINA

I. THIOL REACTORS AS INDUCING AGENTS*

BY

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USING electroretinography in attempts to elucidate the relative significance of aerobic glycolysis and of respiration in the metabolism of the retina in the intact animal, Noell (1951, a, b) found that intravenous injections of sodium iodoacetate—an inhibitor of glycolysis—extinguished within a few minutes electrical response to illumination of the retina in the cat and rabbit. In confirming these findings, Schubert and Bornschein (1951) drew attention to the extensive destruction of the rod and cone and the outer nuclear layers of the retina induced by the iodoacetate injection—observations also recorded by Noell (1952, a, b). That the relationship between changes in the electrical response and histological damage is not direct is seen from the fact that only functional and no anatomical disturbances are observed after injections of azide (Noell, 1952, a), and of sodium fluorite (Babel and Ziv, 1956). The histological damage induced by iodoacetate has been repeatedly confirmed (Karli, 1952 and 1954; de Berardinis and Bonavolontà, 1952; de Berardinis, 1953; and Babel and Ziv, 1956), but the mode of action remains obscure. Remarking on the known ability of iodoacetate to react with thiol groups, Noell (1952, b) observed that many intracellular activities might be affected by this agent. The present investigation was undertaken to determine whether the injurious action upon the retina is shared by other compounds reactive for thiol groups when given intravenously to the rabbit and rat.

Methods and Agents Used

With sodium iodoacetate in a dose of 29 mg./kg. in the rabbit, ophthalmoscopic and histological lesions essentially similar to those reported by previous observers were obtained. Like Karli, we found it unnecessary to give more than one injection. In the rat, a dose of 42 mg./kg. had to be used, but the effect was less consistent, the lesions being either mild or entirely absent.

The various thiol reagents administered are listed in the Table (overleaf). Usually only one injection was given, but some animals received two or three similar injections, generally on consecutive days. The single doses given represented more than 80 per cent. of the minimum lethal dose in nearly every case.

In the rabbit, reagents were injected in the ear vein; in the rat, the injection

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TABLE

THIOL REAGENTS ADMINISTERED INTRAVENOUSLY TO RATS AND RABBITS

Substance	Rats		Rabbits	
	Number Treated	Dose (mg./kg.)	Number Treated	Dose (mg./kg.)
Sodium monobromoacetate	8 1	32 72(*a*)	6 4	32 45(*b*)
Sodium monochloroacetate	2	117(*a*)	3	82
Ethyl iodoacetate	3 6	10 13(*b*)	1	21(*a*)
Iodoacetamide	4	14	3 2	37 67(*b*)
Bromoacetyl bromide			1	81(*a*)
Phenacyl bromide...	3 2	20 24(*b*)	1	5
1-Fluoro 2:6-dinitrobenzene	3	19		
Sodium *p*-chlormercuribenzoate...	6 5	8 11(*b*)	1	19
Mercuric chloride...	2	5		
Sodium arsenite	1	3(*a*)	1	7
3-Amino 4-hydroxyphenyl arsenoxide hydrochloride	2	21(*a*)		
3-Amino 4-hydroxyphenyl dichloroarsine hydrochloride	5 2	20 20(*b*)	1	58(*a*)
Sodium *o*-iodobenzoate	3 3	43 86(*a*)	1	272
Iodine	2 4	6 18(*a*)	1 1	3 3(*a*)
Phenol indo 2:6 dichlorophenol...	3	200(*a*)	1	200(*a*)

Doses were the maximum tolerated as a single injection, except that:

(*a*)=two maximal doses and in a few instances a third maximal or fractional dose.
(*b*)=two or more sub-maximal doses.

was made into the femoral vein through a small incision made under ether anaesthesia. All reagents were made up in aqueous solution or suspension buffered to pH 7·4, concentrations being adjusted to give injection volumes of 2 to 5 ml. in rabbits, and 0·5 to 1·0 ml. in rats. Acids were neutralized with sodium hydroxide; iodine was administered dissolved in propylene glycol.

Ophthalmoscopic examinations were carried out by the direct method in the rabbit, and by the indirect method in the rat. Animals were kept under observation for some 7 to 10 days before being destroyed for histological study. The eyes were fixed in acid Zenker solution: rabbit eyes were usually incised at the

equator and cotton wool wick inserted; rat eyes were fixed intact. Embedding was carried out in paraffin wax, and sections were cut at 5μ.

Results

In the rat, in which sodium iodoacetate produces a mild and inconstant effect, none of the agents used produced any ophthalmoscopic or histological changes. In the rabbit, the results were also negative, except that bromoacetate caused both ophthalmoscopic and histological changes. These changes, obtained with a dose of 32 mg./kg., were similar to those obtained with iodoacetate in doses of 29 mg./kg., differing mainly in being rather milder and largely restricted to the central area. They are described in detail elsewhere in this issue (Lucas, Newhouse, and Davey, 1957).

Discussion

The thiol agents used—including, as they do, heavy metal derivatives, oxidizing agents, and alkylating agents—cover a representative range. That the results in the intact animal were negative except for bromoacetate suggests that the effect is characteristic of iodoacetate and its analogue rather than of thiol reagents as a group. Iodoacetate does not behave like other thiol reagents when used as an enzyme inhibitor (Smythe, 1936) or as a means of inducing developmental anomalies (Hicks, 1953). It can react *in vitro* with the NH_2-group of certain amino-acids (Michaelis and Schubert, 1934) and some of its inhibitory effects are not reversed by addition of thiol compounds (Barron and Singer, 1945). Some thiol-dependent enzyme reactions are inhibited as readily by iodoacetamide as by iodoacetate, yet the neutral amide does not damage the retina, a fact which again points to an unusual mode of action by the parent acid. That the latter is exceptionally effective against phosphoglyceraldehyde dehydrogenase (Cori, Slein, and Cori, 1948), an enzyme of particular importance to a tissue with the high glycolytic activity of retina, may be significant.

While the present work does not indicate that iodoacetate and bromoacetate damage the retina by virtue of being unselective thiol reagents, that possibility cannot be excluded. The influence of such factors as blood-retinal barriers, detoxication processes, and systemic toxicity may be important. As to systemic toxicity, it is of interest that most of the more powerful inhibitors are, in molar terms, too lethal to be administered in dosage comparable with that of sodium iodoacetate. Thus, in the rabbit, the maximal tolerated dosage (millimoles per kg. body weight) of sodium *p*-chloromercuribenzoate or sodium arsenite is 0·050, only a fraction of that of sodium iodoacetate (0·140) or bromoacetate (0·200). Body fluid concentrations of the heavy metal compounds and perhaps of other thiol reagents (*e.g.* phenacyl bromide) high enough to damage the retina may not therefore be feasible. In contrast, however, iodoacetamide, which is no more lethal than sodium iodoacetate, was without effect. These results

would suggest that sodium iodoacetate may owe its effects to a combination of low systemic toxicity and inhibitory properties of a restricted type.

Summary

Sub-lethal doses of a representative group of thiol reagents were injected intravenously into rabbits and rats to determine whether the injurious effect of iodoacetate upon the retina is shown by other inhibitors of sulphydryl enzyme systems. In the rabbit, sodium bromoacetate gave a lesion somewhat similar to that of iodoacetate; all other thiol reagents proved negative. In the rat, bromoacetate was ineffective, as were all other thiol reagents except iodoacetate, which itself produced only a mild and variable effect.

The failure of thiol reagents, other than sodium iodoacetate and bromoacetate, in producing retinal degeneration cannot be related to systemic toxicity alone, for on a molar basis some of the agents were more toxic and others less toxic than iodoacetate. The possibility that iodoacetate and bromoacetate act by virtue of properties other than thiol reactivity is discussed.

We are indebted to Mr. J. B. Davey for some of the ophthalmoscopic observations and to Dr. A. Nakajima for help with this work. We are obliged to the Head of the Chemistry Section, Chemical Defence Experimental Establishment, Porton, for a gift of ethyl iodoacetate and to Messrs. Parke Davis & Co., for the two organic arsenicals used in this study.

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EXPERIMENTAL DEGENERATION OF THE RETINA

II. THE LESION PRODUCED BY BROMOACETATE: OPHTHALMOSCOPIC AND HISTOLOGICAL FEATURES*

BY

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During the course of an investigation of the effects of various thiol reagents upon the rabbit retina (Sorsby, Newhouse, and Lucas, 1957) it was observed that sodium bromoacetate caused histological damage, the details of which are recorded here.

Twelve adult rabbits of mixed stock weighing 1·5 to 2·5 kg. received intravenous injections of from 16 to 32 mg./kg. sodium bromoacetate. In three animals the dose was repeated on the following day. The nine survivors were killed for histological examination 3 to 21 days after injection.

Two animals received combined injections of sodium bromoacetate (16 mg./kg.) and sodium iodoacetate (16 mg./kg.) and were killed 7 days later. All doses are quoted in terms of sodium salt.

The solutions for injection were prepared immediately before use by neutralizing the free acid and making up to volume with phosphate buffer. The eyes were fixed in acid Zenker's solution immediately after death. After removal of the lens, paraffin sections were cut and stained by ordinary haematoxylin and eosin, and by Mallory's phosphotungstic acid haematoxylin.

Observations

Ophthalmoscopic Findings

Retinal haze, probably due to oedema, was usually observed on the day after injection of doses of 32 mg./kg.; 2 days later, this effect had diminished and faint pigment clumping was apparent. By 10 days after injection, the pigmentary disturbance in the mid-ventral region had assumed a cobblestone-like appearance; the central fundus showed many yellow spots, but the area above the disc appeared almost normal. No further changes were observed a week later. After the mixtures of iodoacetate and bromoacetate the appearances were similar.

Histological Findings

(*i*) After single doses of 16–23 mg./kg. of bromoacetate, three rabbits showed no retinal damage.

(*ii*) After two injections of 23 mg./kg. of bromoacetate, one rabbit showed a very localized loss of visual cells in the area centralis when examined a

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week after the second injection. A few pyknotic rod nuclei remained and Müller fibres were seen entering the damaged area. The inner layers were unaffected in this animal.

(*iii*) After single doses of 32 mg./kg. of bromoacetate, five rabbits showed severe retinal damage. In one of these animals, killed three days after injection, many visual cell nuclei were pyknotic and the rods were disintegrated in the area centralis. Numbers of Müller fibres undergoing mitosis were observed in both inner and outer nuclear layers. Occasional pyknotic ganglion cells were seen, and a few bipolar cells were also pyknotic (Fig. 1).

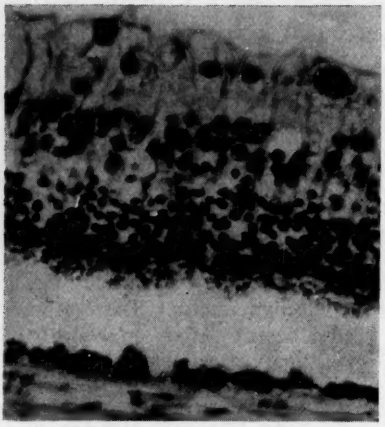
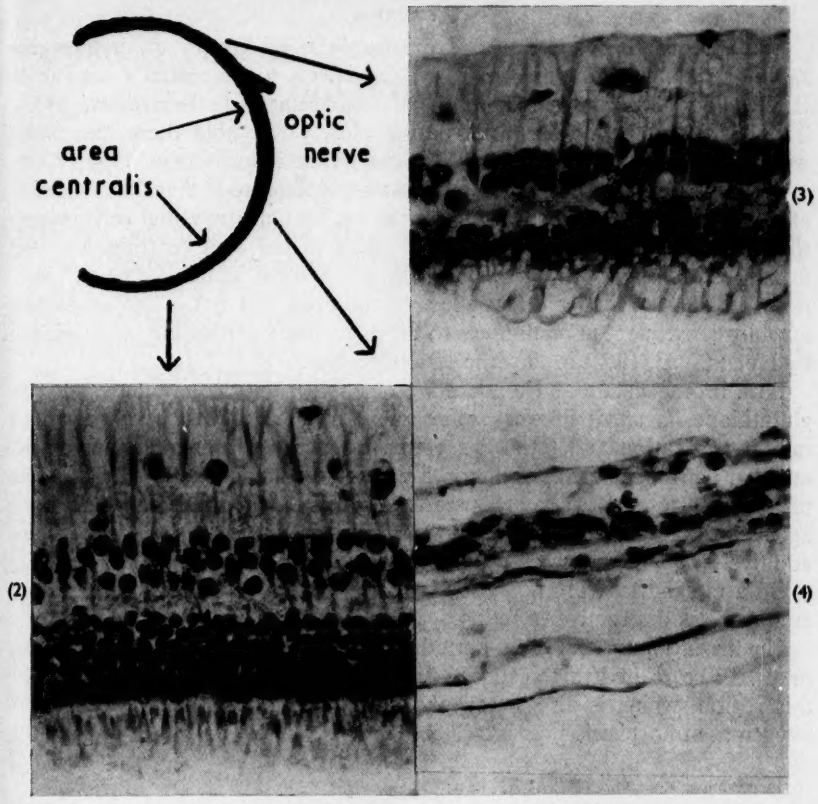


FIG. 1.—Area centralis 3 days after intravenous injection of 32 mg./kg. bromoacetate, showing disintegration and pyknosis of the visual cells and scattered pyknotic nuclei in the bipolar layer. Phosphotungstic acid haematoxylin ×400.

In the right eye, a few visual cells in the mid-dorsal region were also pyknotic. In the other four severely affected animals, killed 7–21 days after injection, very few pyknotic visual cells remained and all layers of the retina had largely disappeared over much of the area centralis (Fig. 4, opposite). The pigmented epithelium was involved in only two animals; continuity was lost and the cells had become entangled amongst the Müller fibre proliferations (Fig. 5, opposite). In three animals there was a small area of necrosis in the visual cell layer of the mid-dorsal region (Fig. 3, opposite). In one animal, foci of lymphocytic infiltration were seen on the choroid.

(*iv*) After the combined injections of 16 mg. each of iodoacetate and bromoacetate, both rabbits showed considerable retinal damage although similar doses of the substances given individually could have been expected to cause, at most, only very mild lesions. In one of the animals, the lesion was both extensive and severe, in the other it was more localized. In the former the pigmented epithelium was extensively involved and infiltrates of lymphocytes were seen in the choroid.



FIGS 2–4.—Mid-dorsal region, area centralis, and peripheral region of one eye (indicated in diagram) showing respectively no changes, slight damage to visual cell layer, and total destruction of the retina 7 days after injection of 32 mg./kg. bromoacetate. Haematoxylin and eosin ×400.

FIG. 5.—Mid-ventral region, showing proliferation of Müller fibres in a damaged area with breaking up and entanglement of pigmented epithelium 16 days after injection of 32 mg./kg. bromoacetate. Phosphotungstic acid haematoxylin ×400.

Discussion

Sodium bromoacetate has not previously been known to damage the rabbit retina. Ophthalmoscopically, the effects are essentially similar to those which follow administration of iodoacetate (de Berardinis, 1953). The histological features of the lesion closely resemble those associated with iodoacetate (Noell, 1952, 1953; Schubert and Bornschein, 1951; Karli, 1952, 1954; de Berardinis, 1953). The main difference is that bromoacetate affects a more limited area of the retina. Although the visual cells appear to be the most susceptible, the other layers in the area centralis are also usually demolished. Since this damage was evident within 7 days of injection, it appears to be a direct effect of the drug and not a late secondary atrophy consequent upon damage to the pigmentary epithelium, as suggested by Noell (1952, 1953) in the case of iodoacetate.

Both bromoacetate and iodoacetate react with thiol compounds, such as glutathione, *in vitro*; in work in progress they have both been shown to inhibit respiration and glycolysis of the isolated retina to a similar extent and the addition of a thiol-donor can reverse some of these effects. The histological resemblances are parallel to the biochemical findings: both agents produce a similar lesion and when given together the effects are additive.

On a molar basis, bromoacetate is somewhat less lethal than iodoacetate and also less destructive to retina.

The finding that damage by both drugs is most severe in the area centralis may well be related to the special functional and metabolic importance of this region, which is also selectively injured in the rabbit by exposure to oxygen at atmospheric pressure (Noell, 1955).

Summary

(1) The intravenous injection of 32 mg./kg. sodium bromoacetate results in necrosis of the area centralis of the rabbit retina.

(2) The histological findings resemble those previously reported after injection of sodium iodoacetate, but the damage is more localized.

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CASE NOTES

ORBITAL CELLULITIS WITH EXUDATIVE RETINAL DETACHMENT*

BY

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EXUDATIVE detachment of the retina in orbital cellulitis is not common and has not often been recorded in the literature (Duke-Elder, 1940, 1952).

The pathogenesis of exudative retinal detachment in orbital cellulitis is due to venous congestion and reactive oedema across the tough fibrous sclera. The detachment is usually not extensive and there is no hole. The vitreous is clear and the treatment is that of orbital cellulitis in general.

Case Report

A boy aged 12 years attended the hospital on September 1, 1956, complaining of pain in the left eye, headache, and bulging of the left eye of rapid onset 10 days before. There was no history of trauma, sinus infection, skin or general infectious disorder, or haemorrhagic diathesis.

The boy was under-nourished, and had a dry skin, and a dry and heavily-coated tongue. Temperature 100° F., pulse 86.

Examination.—Visual acuity in the right eye was 6/9, and in the left counting fingers at 3 m. The left palpebral fissure was narrow, and a horizontal swelling was seen immediately below the left eyebrow. A left proptosis of 10 mm. (right 12 mm.; left 22 mm.) was axial and irreducible, and no alteration could be made by change of posture or pressure on the neck veins (Figure).

FIGURE.—Orbital cellulitis and abscess showing extreme proptosis of 10 mm. The horizontal bulge seen below the left eyebrow is due to the orbital abscess. Fundus examination revealed exudative detachment of retina in the upper part.

The left ocular movements were markedly restricted, and a soft swelling was felt immediately above the left eye. No bruit was heard on auscultation. The conjunctiva was markedly chemosed in the upper part, and the cornea was anaesthetic. The pupil was normal in shape and showed normal reactions. Fundus examination showed dilated veins and exudative retinal detachment in the upper part. No hole could be seen. The confrontation test showed a loss of the lower visual field. A thick-bore needle was

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inserted through the swelling a little above the upper lid, and 1 ml. thick, yellow, creamy pus was withdrawn.

The total leucocyte count was 6,800 per c.mm. (polymorphs 57 per cent., leucocytes 39 per cent., eosinophils 4 per cent.). The erythrocyte sedimentation rate was 54 mm./hr (Westergren). The Kahn test was negative. *X*-rays of the chest, sinuses, orbit, and optic foramen showed no abnormality.

A provisional diagnosis of orbital cellulitis and abscess was made.

Treatment and Follow-up.—The boy was given antibiotic injections, penicillin ophthalmic ointment into the conjunctival sac, and hot fomentations. Next day, the abscess burst through the superior fornix, and a large amount of pus escaped. On the third day, the general condition was markedly improved, the visual acuity improved to 6/12, and the proptosis diminished, although the movements were still markedly restricted, and the detachment had begun to subside.

On the sixth day no detachment was seen, the visual fields were full, and the visual acuity improved to 6/9. There was still 5 mm. of proptosis, but some ocular movements had returned. The erythrocyte sedimentation rate was 27 mm./hr. (Westergren) on September 8.

The patient left the hospital on September 9, 1956. He was advised to report to the follow-up Tuberculosis Clinic for investigation, but did not do so. A month later there was still 2 mm. of proptosis, but there was no detachment of the retina, the ocular movements had markedly improved, and the visual acuity was 6/9. The patient did not complain of any visual disturbances. The eye was normal 6 weeks later.

Aetiology of Exudative Retinal Detachment

The following classification is suggested:

I. PRIMARY EXUDATIVE

(*a*) *Inflammation*

(*i*) Uveitis: Choroiditis, equatorial and anterior, particularly of tuberculous allergic origin, and exudative choroiditis.
(*ii*) Retinitis: Exudative retinitis of Coats (may be chorioretinitis).

(*b*) *Vascular Anomalies*

(*i*) Angiomatosis retinae (von Hippel's disease).
(*ii*) Retinal degeneration with multiple miliary aneurysms.
(*iii*) External haemorrhagic retinitis of Coats.
(*iv*) Trauma in newly-born infants leading to haemorrhage from the outer molecular layer into the subretinal space.

This type of haemorrhagic extravasation is almost indistinguishable from inflammatory exudation by routine fundus examination, except where vascular abnormalities give a clue to the causative lesion.

II. SECONDARY EXUDATIVE

(*a*) *Local Causes*

(*i*) Inflammation leading to reactive oedema across the tough fibrous layer of the sclera.
Inflammation of the orbit (von Graefe, 1863; Berlin, 1866; Becker, 1922).
Orbital cellulitis (Laas, 1901; Holm, 1932).
Scleritis.
Tenonitis of inflammatory origin.
(*ii*) Neoplastic choroidal tumours, malignant melanoma, choroidal metastases (particularly from breast, lungs, and stomach), rarely angioma of choroid.

(*b*) *General Causes.*—These may lead to a generalized rise in venous pressure and may passively affect the choroidal circulation:

(*i*) Toxaemic retinopathy of pregnancy.
(*ii*) Albuminuric retinopathy.
(*iii*) Malignant hypertension.

It may be that, in addition to the rise in venous pressure, certain other toxins hitherto unidentified, such as histamines, may have an important role in the causation of retinal detachment. Cardiac lesions causing a rise in venous pressure are unlikely to be responsible for the detachment.

The diminution of vision in orbital abscess may be due to several causes:

(*a*) Mechanical pressure on the nerve fibres of the optic nerve, so that their conductivity is interfered with. If the pressure is relieved early (as it was in the case reported above), complete and almost immediate recovery of vision follows. Ophthalmoscopy is likely to show only dilated veins.

(*b*) Compression of the vascular tree supplying the optic nerve. In extreme cases the fundus picture may resemble that of obstruction of central retinal artery.

(*c*) Inflammation of the vascular tree leading to dramatic loss of vision and early atrophy (Eagleton, 1935).

(*d*) Inflammation of the nerve leading to retrobulbar or optic neuritis. If this lasts for some time, small necrotic areas may appear (Bartels, 1906). This may cause a positive Marcus Gunn pupillary phenomenon, and fundus examination may reveal optic neuritis or extreme swelling resembling papilloedema, or there may be little evidence at the nervehead. Recovery of vision will not be so rapid as in (*a*) above.

It may be said that the nerve fibres of the pupillary pathways are affected early in cases of inflammation (as in retrobulbar neuritis) but later in cases of compression. In the case reported above, all the pupillary reactions were normal.

The abscess, once formed, tends to follow the path of least resistance; in the case of an abscess within the periosteum, the fornices may be perforated, while in the case of a subperiosteal abscess, the skin is the favourite site. In this case, the abscess burst through the superior conjunctival fornix. The greatest difficulties are encountered in abscesses of the central compartment, where symptoms may resemble those of meningeal irritation.

Summary

A case of orbital cellulitis and abscess with exudative retinal detachment is described. There was a marked loss of vision, but this was rapidly restored on evacuation of the pus. It appears, therefore, that mechanical pressure on the nerve fibres was a cause of marked diminution of vision. The abscess in this case burst through the superior fornix. The retinal detachment subsided rapidly on the fifth day after admission.

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OBITUARY

SIR JAMSHEDJI DUGGAN (1884–1957)

By the sudden death of Colonel Sir Jamshedji Nasarwanji Duggan on January 15, 1957, ophthalmology has lost one of its international figures and India her most distinguished ophthalmic surgeon.

Born in Bombay, he graduated in medicine from the Grant Medical College in 1904, and after holding various post-graduate posts joined the C.J. Ophthalmic Hospital as clinical registrar in 1906, being appointed to the newly-created post of tutor in ophthalmology. He completed his post-graduate education by travelling in Europe from 1908–12, studying in Vienna under Fuchs, in Wiesbaden under Pagenstecher, and then in London under Treacher Collins and Parsons. He returned to England in 1912 to take the D.O.(Oxon). Thereafter he conducted a large practice in Bombay, becoming superintendent of the C.J. Ophthalmic Hospital, and Professor of Ophthalmology in 1923, a post which he held until his retirement in 1939. During this period he brought the hospital to a high standard of efficiency, enlarging the building and conducting courses of post-graduate teaching. From 1940–45 he was superintendent of the Tata Memorial Hospital for Cancer. Elected a Fellow of the University of Bombay in 1918, he became Dean of the Faculty of Medicine in 1929. He was elected a Fellow of the College of Physicians and Surgeons of that city in 1918, and became its President in 1934. In 1929 he introduced higher degrees and diplomas in ophthalmology in both the University of Bombay and the College of Physicians and Surgeons, and a quarter of a century later he was largely instrumental in introducing the M.S. degree in ophthalmology into the University on lines similar to the corresponding degree in the University of London.

In addition to these numerous and responsible professional activities in civil life, Duggan's military career was outstanding. In the first world war he held the honorary rank of Major in the Indian Medical Service and was consultant ophthalmic surgeon to all the war hospitals in Bombay. His activities in the second world war, during which he was promoted to the rank of Colonel, were equally responsible, and he acted as President of the Joint War Committee of the Bombay branch of the Red Cross Society and the Order of St. John of Jerusalem.

His professional qualities met with their due recognition. In 1934 he was elected President of the All-India Ophthalmological Society, and for many years represented India on the editorial committee of this Journal. A frequent figure at international congresses, he became the representative of Asia on the International Council of Ophthalmology in 1950.

He was equally enthusiastic in social and public work, taking a very active part in various societies and charities for the prevention of blindness and the assistance of the blind. In 1916 he became a Justice of the Peace in Bombay, in 1918 a Magistrate, and in 1943 a Sheriff of that city. In 1929 he was awarded the O.B.E. and in 1933 became a C.I.E.; in 1936 he was knighted, and in 1944 became a Knight of the British Empire. A man of great social charm, he was much interested in the Rotary movement and was also an enthusiastic member of the Western India Turf Club. His sudden death is without any doubt a great tragedy for Indian ophthalmology, and his sage and wise advice will be greatly missed. His death also is a personal loss to his many ophthalmic friends throughout the world, whose sympathy will go out to his charming and gracious widow, who helped him so greatly and constantly in his professional and social life, and to his two sons.